

### 15.0.2 Subjects in Tirofiban + Heparin group with serious adverse events (SAEs)

Table 15.0.2.1 SAEs in the tirofiban +heparin group from the phase III trials (cont).

| Protocol/<br>Subject #         | Age/ Sex | Day of Onset     | Adverse Experience                                                                           | Action | Outcome    |
|--------------------------------|----------|------------------|----------------------------------------------------------------------------------------------|--------|------------|
| <b>TIROFIBAN +<br/>HEPARIN</b> |          |                  |                                                                                              |        |            |
| <b>RESTORE TRIAL</b>           |          |                  |                                                                                              |        |            |
| 013-013 3183                   | 41 F     | 1<br>1<br>1<br>2 | Ecchymosis<br>Bleeding, postoperative<br>Pain, chest<br>Cardiovascular hemodynamics abnormal | D/C'd  | Recovered  |
| 013-013 3195                   | 66 M     | 3                | Ventricular fibrillation                                                                     | None   | Recovered  |
| 013-014 1839                   | 76 F     | 14               | Pain, chest                                                                                  | None   | Recovered  |
| 013-014 1841                   | 51 M     | 16               | Vascular disorder                                                                            | None   | Recovered  |
| 013-014 1844                   | 69 M     | 1                | GI hemorrhage                                                                                | D/C'd  | Recovered  |
| 013-014 1848                   | 57 M     | 1                | Cardiac tamponade                                                                            | D/C'd  | Recovered  |
| 013-014 2380                   | 74 F     | 3                | Atrial fibrillation                                                                          | None   | Continuing |
|                                |          | 13               | Shock, cardiogenic                                                                           | None   | Recovered  |
| 013-014 2762                   | 75 F     | 25               | Pain, chest                                                                                  | None   | Recovered  |
|                                |          | 25               | Dyspnea                                                                                      |        |            |
|                                |          | 25               | Transient ischemic attack                                                                    |        |            |
| 013-014 2765                   | 67 F     | 4                | Hemorrhage                                                                                   | None   | Recovered  |
|                                |          | 5                | Supraventricular tachycardia                                                                 |        |            |
|                                |          | 5                | Shock, septic                                                                                |        |            |
|                                |          | 5                | Death                                                                                        |        |            |
| 013-014 3250                   | 73 F     | 3                | Death                                                                                        | None   | Death      |
| 013-014 3760                   | 71 M     | 3                | Angina, unstable                                                                             | None   | Recovered  |
|                                |          | 12               | Ulcer, peptic                                                                                |        |            |
| 013-014 3762                   | 44 M     | 22               | Angina, unstable                                                                             | None   | Recovered  |
| 013-014 3996                   | 75 F     | 1                | Hemorrhage                                                                                   | D/C'd  | Continuing |
| 013-018 1861                   | 70 M     | 1                | Hematuria                                                                                    | D/C'd  | Recovered  |
|                                |          | 19               | Drug overdose<br>Angina pectoris                                                             |        |            |
| 013-019 1114                   | 67 F     | 1                | Ventricular fibrillation                                                                     | None   | Recovered  |
|                                |          | 1                | Ventricular tachycardia                                                                      |        |            |
| 013-020 1592                   | 43 M     | 1                | Dissection, coronary artery                                                                  | None   | Recovered  |
| 013-020 1594                   | 61 M     | 1                | Dissection, coronary artery                                                                  | D/C'd  | Recovered  |
| 013-021 1266                   | 48 M     | 11               | CVA                                                                                          | None   | Continuing |
| 013-021 1809                   | 73 M     | 1                | Shock, cardiogenic                                                                           | D/C'd  | Death      |
|                                |          | 1                | Rupture, artery                                                                              |        |            |
|                                |          | 1                | Cardiac tamponade                                                                            |        |            |
|                                |          | 1                | Hemorrhage                                                                                   |        |            |
|                                |          | 1                | Hypotension                                                                                  |        |            |
|                                |          | 1                | Death                                                                                        |        |            |
| 013-021 2708                   | 77 F     | 1                | Death                                                                                        | None   | Death      |
|                                |          | 1                | Hypotension                                                                                  |        |            |
|                                |          | 1                | Ventricular fibrillation                                                                     |        |            |
| 013-022 3102                   | 62 M     | 1                | Dissection, coronary artery                                                                  | D/C'd  | Recovered  |
|                                |          | 1                | Effusion, pericardial                                                                        |        |            |
|                                |          | 1                | Shock, cardiogenic                                                                           |        |            |
|                                |          | 1                | Hypotension                                                                                  |        |            |
|                                |          | 2                | Respiratory distress syndrome                                                                |        |            |
| 013-025 1939                   | 73 F     | 3                | Pain, abdominal                                                                              | None   | Recovered  |
|                                |          | 15               | Mental status change                                                                         |        |            |
| 013-026 1991                   | 41 M     | 3                | Pain, chest                                                                                  | None   | Recovered  |
| 013-026 3651                   | 55 M     | 17               | Embolism/infarction, pulmonary                                                               | None   | Recovered  |

## 15.0.2 Subjects in Tirofiban + Heparin group with serious adverse events (SAEs)

Table 15.0.2.1 SAEs in the tirofiban theparin group from the phase III trials (cont).

| Protocol/<br>Subject #                           | Age/ Sex | Day of Onset         | Adverse Experience                                 | Action | Outcome                               |
|--------------------------------------------------|----------|----------------------|----------------------------------------------------|--------|---------------------------------------|
| <b>TIROFIBAN +<br/>HEPARIN<br/>RESTORE TRIAL</b> |          |                      |                                                    |        |                                       |
| 013-027 2029                                     | 58 M     | 2<br>28              | Drug overdose<br>Myocardial infarction             | None   | Recovered                             |
| 013-027 3302                                     | 49 M     | 1                    | Blood pressure decreased                           | None   | Recovered                             |
| 013-027 3327                                     | 74 M     | 7                    | Pain, chest                                        | None   | Recovered                             |
| 013-028 1645                                     | 54 M     | 29<br>29             | Hypertension<br>Heart failure                      | None   | Recovered                             |
| 013-028 1649                                     | 62 F     | 23                   | Pain, chest                                        | None   | Recovered                             |
| 013-029 2023                                     | 59 F     | 23                   | Thrombosis                                         | None   | Recovered                             |
| 013-030 1106                                     | 83 M     | 1                    | Bleeding, postoperative                            | D/C'd  | Continuing                            |
| 013-030 1439                                     | 55 M     | 9                    | Herniorrhaphy                                      | None   | Recovered                             |
| 013-030 2093                                     | 47 M     | 1                    | Dissection, coronary artery                        | None   | Recovered                             |
| 013-030 3343                                     | 68 F     | 6<br>13              | Heart failure<br>Sinus tachycardia                 | None   | Recovered                             |
| 013-031 1826                                     | 66 M     | 5<br>8               | Transient ischemic attack<br>Cholecystitis         | None   | Recovered                             |
| 013-031 1994                                     | 72 M     | 18                   | Peripheral vascular disorder                       | None   | Recovered                             |
| 013-031 2741                                     | 46 M     | 25<br>25<br>25       | Anxiety<br>Pain, chest<br>Dizziness                | None   | Recovered                             |
| 013-032 2330                                     | 63 M     | 18<br>29             | CVA<br>Atrial fibrillation                         | None   | Recovered                             |
| 013-032 3015 75                                  | 75 F     | 3                    | Allergy, contrast medium                           | None   | Recovered                             |
| 013-037 1789                                     | 44 M     | 2                    | Septicemia                                         |        |                                       |
| 013-038 1203                                     | 55 M     | 2                    | Septicemia                                         | None   | Recovered                             |
| 013-038 1206                                     | 56 M     | 1                    | Fever                                              | None   | Recovered                             |
| 013-038 1207                                     | 64 M     | 3                    | Discomfort, pharyngeal                             | None   | Recovered                             |
| 013-039 1340                                     | 64 F     | 9                    | Pseudoaneurysm                                     | None   | Recovered                             |
| 013-039 2675                                     | 45 M     | 6                    | Heart failure                                      | None   | Recovered                             |
| 013-041 1211                                     | 58 F     | 2<br>2               | Hypotension<br>Bleeding, postoperative             | D/C'd  | Recovered                             |
| 013-041 2072                                     | 70 M     | 1                    | Dissection, coronary artery                        | D/C'd  | Recovered                             |
| 013-041 2074                                     | 56 M     | 8                    | Pain, chest                                        | None   | Recovered                             |
| 013-041 2075                                     | 61 F     | 25<br>25<br>25<br>25 | Pain, chest<br>Pain, neck<br>Anxiety<br>Depression | None   | Recovered<br><br><br>Continuing       |
| 013-042 1341                                     | 70 F     | 17                   | Thrombosis, deep vein                              | None   | Recovered                             |
| 013-045 1313                                     | 48 F     | 1                    | Dissection, coronary artery                        | None   | Recovered                             |
| 013-046 2009                                     | 77 F     | 18                   | Pain, chest                                        | None   | Recovered                             |
| 013-046 2409                                     | 76 M     | 2<br>30              | Hemorrhage<br>Dehydration                          | None   | Recovered                             |
| 013-046 2642                                     | 77 F     | 1<br>5               | Hematoma<br>Thrombosis, deep vein                  | D/C'd  | Recovered                             |
| 013-047 2105                                     | 66 F     | 19<br>20<br>20       | Pain, chest<br>Diabetes mellitus<br>Cellulitis     | None   | Recovered<br>Continuing<br>Continuing |
| 013-047 2154                                     | 43 M     | 23                   | Vascular disorder                                  | None   | Recovered                             |

## 15.0.2 Subjects in Tirofiban + Heparin group with serious adverse events (SAEs)

Table 15.0. 1 SAEs in the tirofiban + heparin group from the phase III trials (cont).

| Protocol/<br>Subject #         | Age/ Sex | Day of Onset                     | Adverse Experience                                                                                                               | Action | Outcome                                                                                  |
|--------------------------------|----------|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------|--------|------------------------------------------------------------------------------------------|
| <b>TIROFIBAN +<br/>HEPARIN</b> |          |                                  |                                                                                                                                  |        |                                                                                          |
| <b>RESTORE TRIAL</b>           |          |                                  |                                                                                                                                  |        |                                                                                          |
| 013-048 2052                   | 44 F     | 1                                | CVA                                                                                                                              | None   | Recovered                                                                                |
| 013-049 1382                   | 55 F     | 1<br>2<br>20                     | Dissection, coronary artery<br>Pseudoaneurysm<br>Pain, chest                                                                     | D/C'd  | Recovered                                                                                |
| 013-049 1384                   | 54 M     | 1                                | Dissection, coronary artery                                                                                                      | None   | Recovered                                                                                |
| 013-049 1386                   | 63 M     | 8<br>14<br>15                    | Pain, chest<br>Hemorrhage<br>Hemorrhage, retroperitoneal                                                                         | None   | Recovered                                                                                |
| 013-049 1388                   | 71 M     | 3                                | Pseudoaneurysm                                                                                                                   | None   | Recovered                                                                                |
| 013-050 1482                   | 69 F     | 11                               | Pericarditis                                                                                                                     | None   | Recovered                                                                                |
| 013-051 1054                   | 65 M     | 4                                | GI hemorrhage                                                                                                                    | None   | Recovered                                                                                |
| 013-052 1701                   | 73 M     | 1                                | Dissection, coronary artery                                                                                                      | None   | Recovered                                                                                |
| 013-052 1704                   | 76 F     | 1<br>4<br>24<br>24               | Hematoma<br>Hemorrhage<br>Dizziness<br>Dehydration                                                                               | None   | Recovered                                                                                |
| 013-052 1706                   | 72 F     | 1<br>3                           | Bradycardia<br>Respiratory distress                                                                                              | None   | Recovered                                                                                |
| 013-052 1706                   | 72 F     | 3<br>3<br>3<br>3                 | Hypotension<br>Asystole<br>Heart failure<br>Ventricular tachycardia                                                              | None   | Recovered                                                                                |
| 013-053 1479                   | 75 M     | 1<br>6<br>8<br>8<br>9<br>9<br>18 | Hypotension<br>Pain, chest<br>Hemorrhage, gastrointestinal<br>CVA<br>Ventricular tachycardia<br>Asystole<br>Mental status change | None   | Recovered<br>Recovered<br>Recovered<br>Continuing<br>Recovered<br>Recovered<br>Recovered |
| 013-053 2292                   | 57 M     | 2                                | Drug overdose                                                                                                                    | None   | Recovered                                                                                |
| 013-053 2296                   | 78 F     | 9                                | Angina, unstable                                                                                                                 | None   | Recovered                                                                                |
| 013-053 2298                   | 67 F     | 21                               | Neoplasm, thyroid, malignant                                                                                                     | None   | Recovered                                                                                |
| 013-053 2300                   | 72 M     | 1<br>2                           | Neuropathy, median nerve<br>Peripheral pulse decreased                                                                           | None   | Continuing                                                                               |
| 013-055 1036                   | 58 F     | 1                                | Dissection, coronary artery                                                                                                      | D/C'd  | Recovered                                                                                |
| 013-055 1999                   | 48 M     | 5<br>9                           | Transient ischemic attack<br>Occlusion, arterial, LWR. extrem.                                                                   | None   | Continuing<br>Resolved                                                                   |
| 013-055 2003                   | 44 M     | 2                                | Hemorrhage, retroperitoneal                                                                                                      | None   | Continuing                                                                               |
| 013-055 2888                   | 55 M     | 1                                | Dissection, coronary artery                                                                                                      | D/C'd  | Recovered                                                                                |
| 013-056 1763                   | 73 M     | 3                                | Occlusion, coronary artery                                                                                                       | None   | Recovered                                                                                |
| 013-058 1181                   | 40 M     | 5                                | Occlusion, coronary artery                                                                                                       | None   | Recovered                                                                                |
| 013-058 1183                   | 53 M     | 1                                | Dissection, coronary artery                                                                                                      | D/C'd  | Recovered                                                                                |
| 013-058 1188                   | 77 M     | 9                                | Occlusion, coronary artery                                                                                                       | None   | Recovered                                                                                |
| 013-058 I 190                  | 73 M     | 3                                | Cardiac arrest                                                                                                                   | None   | Recovered                                                                                |
| 013-060 1167                   | 59 M     | 1                                | Dissection, coronary artery                                                                                                      | None   | Recovered                                                                                |
| 013-060 1910                   | 53 M     | 13                               | Syncope                                                                                                                          | None   | Recovered                                                                                |
| 013-060 1911                   | 68 F     | 2                                | Fever                                                                                                                            | None   | Recovered                                                                                |
| 013-060 2992                   | 71 F     | 24<br>24                         | Fever<br>Infection, urinary tract                                                                                                | None   | Recovered                                                                                |

## 15.0.2 Subjects in Tirofiban + Heparin group with serious adverse events (SAEs)

Table 15.0.2.1 SAEs in the tirofiban +heparin group from the phase III trials (cont).

| Protocol/<br>Subject #         | Age/ Sex | Day of Onset | Adverse Experience             | Action | Outcome    |
|--------------------------------|----------|--------------|--------------------------------|--------|------------|
| <b>TIROFIBAN +<br/>HEPARIN</b> |          |              |                                |        |            |
| <i>RESTORE Trial</i>           |          |              |                                |        |            |
| 013-060 3164                   | 73 M     | 2            | Infection, bacterial           | None   | Recovered  |
| 013-061 1816                   | 49 F     | 3            | Ecchymosis                     | None   | Recovered  |
|                                |          | 6            | Pain, chest                    |        |            |
| 013-062 1416                   | 67 M     | 2            | Thrombocytopenia               | None   | Recovered  |
| 013-062 2661                   | 55 F     | 1            | Rupture, artery                | D/C'd  | Recovered  |
| 013-062 2979                   | 59 M     | 23           | Pain, chest                    | None   | Continuing |
| 013-062 2989                   | 53 F     | 4            | Hypesthesia                    | None   | Recovered  |
|                                |          | 25           | Pain, ear                      |        |            |
|                                |          | 25           | Hypesthesia                    |        |            |
| 013-062 3932                   | 72 M     | 1            | Dissection, coronary artery    | None   | Recovered  |
| 013-062 3940                   | 67 F     | 28           | Pain, chest                    | None   | Continuing |
| 013-062 3942                   | 76 M     | 20           | Embolism/infarction, pulmonary | None   | Recovered  |
| 013-064 1777                   | 72 M     | 2            | Hemorrhage, retroperitoneal    | D/C'd  | Death      |
|                                |          | 10           | Embolism/infarction, pulmonary |        |            |
|                                |          | 11           | Death                          |        |            |
| 013-064 2456                   | 69 M     | 19           | Pain, chest                    | None   | Recovered  |
| 013-064 2492                   | 37 F     | 6            | Pain, chest                    | None   | Recovered  |
| 013-067 2015                   | 55 F     | 29           | Pain, chest                    | None   | Recovered  |
| 013-069 2242                   | 64 F     | 5            | Pain, chest                    | None   | Recovered  |
| 013-069 2537                   | 71 F     | 1            | Dissection, coronary artery    | D/C'd  | Recovered  |
| 013-069 3279                   | 66 M     | 1            | Ventricular fibrillation       | None   | Recovered  |
| 013-069 3371                   | 57 M     | 7            | Pain, chest                    | None   | Recovered  |
| 013-070 2450                   | 48 M     | 13           | Angina, unstable               | None   | Recovered  |
| 013-070 2453                   | 54 M     | 1            | Drug overdose                  | None   | Continuing |
|                                |          | 30           | Hemorrhage, gastrointestinal   |        |            |
| 013-071 2595                   | 44 F     | 6            | Infection, urinary tract       | None   | Continuing |
| 013-073 3806                   | 75 F     | 11           | Pain, back                     | None   | Recovered  |
| 013-076 1513                   | 76 M     | 22           | Death                          | None   | Death      |
|                                |          | 22           | Arrhythmia                     |        |            |
| 013-076 1520                   | 70 M     | 8            | Pain, chest                    | None   | Recovered  |
|                                |          | 8            | Dissection, coronary artery    |        |            |
|                                |          | 17           | Pain, chest                    |        |            |
| 013-077 1532                   | 56 M     | 1            | Drug overdose                  | None   | Recovered  |
| 013-077 1534                   | 71 M     | 1            | Drug overdose                  | None   | Recovered  |
| 013-077 1536                   | 62 M     | 1            | Drug overdose                  | None   | Recovered  |
|                                |          | 11           | Pain, chest                    |        |            |
| 013-077 1538                   | 61 M     | 1            | Drug overdose                  | None   | Recovered  |
| 013-077 1692                   | 72 M     | 1            | Drug overdose                  | None   | Recovered  |
| 013-077 1694                   | 51 M     | 1            | Drug overdose                  | None   | Recovered  |
| 013-077 1694                   | 51 M     | 21           | Pain, chest                    | None   | Recovered  |
| 013-077 1695                   | 62 M     | 1            | Drug overdose                  | None   | Recovered  |
|                                |          | 5            | Pain, chest                    |        |            |
|                                |          | 9            | Infection, bacterial           |        |            |
| 013-078 2065                   | 70 F     | 2            | Bursitis                       | None   | Recovered  |
|                                |          | 13           | Pain, musculoskeletal          |        |            |
| 013-079 2397                   | 64 M     | 22           | Cardiac arrest                 | None   | Recovered  |
|                                |          | 22           | Shock, cardiogenic             |        |            |
|                                |          | 22           | Dissection, coronary artery    |        |            |
| 013-080 1504                   | 65 F     | 1            | Dissection, coronary artery    | D/C'd  | Recovered  |
| 013-080 1921                   | 54 M     | 8            | Pain, chest                    | None   | Continuing |
| 013-080 1925                   | 61 M     | 1            | Dissection, coronary artery    | D/C'd  | Recovered  |

## 15.0.2 Subjects in Tirofiban + Heparin group with serious adverse events (SAEs)

Table 15.0.2.1 SAEs in the tirofiban +heparin group from the phase III trials (cont).

| Protocol/<br>Subject #         | Age/ Sex | Day of Onset | Adverse Experience              | Action | Outcome    |
|--------------------------------|----------|--------------|---------------------------------|--------|------------|
| <b>TIROFIBAN +<br/>HEPARIN</b> |          |              |                                 |        |            |
| <i>RESTORE Trial</i>           |          |              |                                 |        |            |
| 013-083 2488                   | 46 M     | 29           | Pain, chest                     | None   | Recovered  |
| 013-083 3238                   | 73 M     | 7            | Pneumonia                       | None   | Recovered  |
| 013-085 3263                   | 65 M     | 4            | CVA                             | None   | Continuing |
| 013-085 3854                   | 47 F     | 23           | Pain, chest                     |        |            |
| 013-087 2218                   | 71 F     | 1            | Confusion                       | None   | Continuing |
| 013-087 2786                   | 42 M     | 1            | Occlusion, coronary artery      | D/C'd  | Continuing |
|                                |          | 1            | Dissection, coronary artery     |        |            |
| 013-088 2516                   | 75 F     | 3            | Hemorrhage, retroperitoneal     | None   | Recovered  |
| 013-088 3731                   | 40 M     | 1            | Dissection, coronary artery     | D/C'd  | Recovered  |
| 013-089 2061                   | 74 F     | 13           | Angina pectoris                 | None   | Recovered  |
| 013-089 2562                   | 47 F     | 2            | Vascular disorder               | None   | Recovered  |
|                                |          | 29           | Angina, unstable                |        |            |
| 013-089 2566                   | 71 M     | 2            | Hemorrhage, retroperitoneal     | None   | Recovered  |
| 013-089 3907                   | 44 M     | 22           | Angina, unstable                | None   | Recovered  |
| 013-090 2416                   | 59 F     | 3            | Angina pectoris                 | None   | Recovered  |
| 013-091 2861                   | 58 F     | 1            | Dissection, coronary artery     | D/C'd  | Recovered  |
| 013-095 1542                   | 47 M     | 10           | Pain, chest                     | None   | Recovered  |
| 013-095 1545                   | 65 M     | 1            | Dissection, coronary artery     | D/C'd  | Recovered  |
| 013-098 2437                   | 75 M     | 2            | Melena                          | D/C'd  | Recovered  |
| 013-098 2437                   | 75 M     | 8            | Myocardial infarction           | None   | Continuing |
|                                |          | 8            | Occlusion, coronary artery      |        |            |
|                                |          |              | Dissection, coronary artery     | None   | Recovered  |
| 013-100 1200                   | 61 M     |              | Dissection, coronary artery     | None   | Recovered  |
| 013-100 2805                   | 66 F     | 1            | Dissection, coronary artery     | None   | Recovered  |
| 013-101 2203                   | 67 M     | 6            | Pain, chest                     | None   | Continuing |
| 013-101 2212                   | 68 M     | 1            | Dissection, coronary artery     | D/C'd  | Death      |
|                                |          | 2            | Confusion                       |        |            |
|                                |          | 6            | Heart failure                   |        |            |
|                                |          | 6            | Ventricular tachycardia         |        |            |
|                                |          | 7            | Shock, cardiogenic              |        |            |
|                                |          | 8            | Death                           |        |            |
| 013-101 2214                   | 67 M     | 1            | Dissection, coronary            | D/C'd  | Recovered  |
| 013-101 2794                   | 35 M     | 4            | Pain, chest                     | None   | Recovered  |
| 013-101 2797                   | 68 F     | 4            | Pain, chest                     |        |            |
| 013-101 3315                   | 50 M     | 24           | Pain, chest                     | None   | Recovered  |
| 013-101 4006                   | 54 M     | 20           | Pain, chest                     | None   | Recovered  |
|                                |          | 30           | Atrial fibrillation             |        |            |
| 013-103 5604                   | 67 M     | 7            | Ventricular tachycardia         | None   | Recovered  |
| 013-103 5607                   | 67 F     | 1            | Pancreatitis                    | None   | Recovered  |
| 013-104 5009                   | 63 M     | 1            | Dissection, aortic              | D/C'd  | Recovered  |
|                                |          | 1            | Dissection, coronary artery     |        | Continuing |
| 013-105 5806                   | 75 M     | 4            | Angina, unstable                | None   | Recovered  |
| 013-105 5818                   | 76 M     | 20           | Embolism/infarction, pulmonary  | None   | Recovered  |
| 013-106 5202                   | 51 M     | 1            | Dissection, coronary artery     | D/C'd  | Recovered  |
| 013-106 5202                   | 51 M     | 6            | Angina pectoris                 | None   | Recovered  |
|                                |          | 9            | Angina pectoris                 |        |            |
| 013-106 5205                   | 59 M     | 17           | Neoplasm, esophageal, malignant | None   | Continuing |
| 013-110 5051                   | 57 M     | 1            | Hemopericardium                 | D/C'd  | Recovered  |
|                                |          | 1            | Dissection, coronary artery     |        | Continuing |
|                                |          | 2            | Shock, cardiogenic              |        | Recovered  |
|                                |          | 9            | Ulcer, gastric w/hemorrhage     |        | Continuing |

## 15.0.2 Subjects in Tirofiban + Heparin group with serious adverse events (SAEs)

Table 15.0.2.1 SAEs in the tirofiban + heparin group from the phase III trials (cont).

| Protocol/<br>Subject #         | Age/ Sex | Day of Onset | Adverse Experience        | Action | Outcome    |
|--------------------------------|----------|--------------|---------------------------|--------|------------|
| <b>TIROFIBAN +<br/>HEPARIN</b> |          |              |                           |        |            |
| <i>RESTORE Trial</i>           |          |              |                           |        |            |
| 013-114 5265                   | 67 F     | 1<br>22      | Hematoma<br>Heart failure | D/C'd  | Recovered  |
| 013-114 5267                   | 55 M     | 5            | Angina pectoris           | None   | Recovered  |
| 013-114 5279                   | 79 F     | 18           | Angina pectoris           | None   | Recovered  |
| 013-115 5650                   | 58 M     | 1            | Fistula, arteriovenous    | None   | Continuing |
| 013-118 3656                   | 62 M     | 7            | Gastritis                 | None   | Continuing |
| 013-118 3659                   | 74 M     | 18           | Atrial fibrillation       | None   | Continuing |
| 013-119 2832                   | 80 M     | 21 2         | Urinary retention         | None   | Recovered  |
| 013-119 2833                   | 52 M     | 1            | Drug overdose             | None   | Recovered  |
| 013-119 3645                   | 47 M     | 15           | Angina pectoris           | None   | Recovered  |
| 013-119 3812                   | 70 F     | 3            | Pain, arm                 | None   | Recovered  |
| 013-119 3815                   | 65 F     | 2            | Arteriovenous fistula     | None   | Recovered  |
| 013-120 3664                   | 52 F     | 9            | Angina, unstable          | None   | Recovered  |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials.

| Protocol/<br>Subject #  | Age/ Sex | Day of Onset         | Adverse Experience                                                                       | Action | Outcome    |
|-------------------------|----------|----------------------|------------------------------------------------------------------------------------------|--------|------------|
| <b>HEPARIN ALONE</b>    |          |                      |                                                                                          |        |            |
| <b>PRISM-PLUS Trial</b> |          |                      |                                                                                          |        |            |
| 006-004 5066            | 61 M     | 9                    | Infection, urinary tract                                                                 | None   | Recovered  |
| 006-004 5465            | 64 M     | 1                    | Fever                                                                                    | None   | Recovered  |
| 006-008 50 14           | 69 M     | 2                    | Drug overdose                                                                            | None   | Recovered  |
| 006-008 5141            | 62 M     | 7<br>7               | Death<br>Shock, cardiogenic                                                              | None   | Death      |
| 006-008 5 145           | 75 M     | 6                    | Asystole                                                                                 | None   | Recovered  |
| 006-008 5375            | 77M      | 23                   | Infection, bone/cartilage                                                                | None   | Recovered  |
| 006-008 5377            | 37 M     | 11                   | Pain, chest                                                                              | None   | Recovered  |
| 006-008 5394            | 41 M     | 1                    | Drug overdose                                                                            | None   | Recovered  |
| 006-010 5173            | 74 M     | 13                   | Cellulitis                                                                               | None   | Recovered  |
| 006-011 5078            | 76 M     | 23                   | Edema/swelling                                                                           | None   | Recovered  |
| 006-011 5388            | 62 M     | 27                   | Gastroenteritis                                                                          | None   | Recovered  |
| 006-026 5032            | 69 M     | 1<br>6<br>18<br>18   | Heart failure<br>Respiratory failure<br>Respiratory failure<br>Thrombosis, deep vein     | None   | Recovered  |
| 006-029 1211            | 61 M     | 2                    | Pneumonia                                                                                | None   | Recovered  |
| 006-029 6475            | 64 M     | 15<br>4              | Pneumonia<br>Heart failure                                                               | None   | Recovered  |
| 006-029 6480            | 63 M     | 2                    | Pneumonia                                                                                | None   | Recovered  |
| 006-029 648 1           | 49 M     | 11<br>1              | Heart failure<br>Drug overdose                                                           | None   | Recovered  |
| 006-032 1029            | 66 M     | 3                    | Respiratory insufficiency                                                                | None   | Recovered  |
| 006-032 6013            | 46 M     | 1                    | Drug overdose                                                                            | None   | Recovered  |
| 006-032 6669            | 69 F     | 3                    | Phlebitis/thrombophlebitis                                                               | None   | Recovered  |
| 006-033 6132            | 49 F     | 1                    | Drug overdose                                                                            | None   | Recovered  |
| 006-033 6165            | 53 F     | 23                   | Pain, chest                                                                              | None   | Recovered  |
| 006-033 6771            | 70 M     | 13<br>12             | Death<br>Shock, cardiogenic                                                              | None   | Death      |
| 006-033 6815            | 71 M     | 4<br>10<br>17<br>3   | Edema, pulmonary<br>Edema, pulmonary<br>Edema, pulmonary<br>Valvular disorder            | None   | Recovered  |
| 006-034 1022            | 68 M     | 22                   | Renal insufficiency                                                                      | None   | Recovered  |
| 006-034 1054            | 75 F     | 11<br>1              | Death<br>Edema, pulmonary                                                                | None   | Recovered  |
| 006-034 1619            | 70 F     | 9                    | Angina, unstable                                                                         | None   | Recovered  |
| 006-034 6007            | 63 M     | 24<br>24             | Embolism/infarction, pulmonary<br>Thrombosis, deep vein                                  | None   | Recovered  |
| 006-034 6981            | 75 M     | 25<br>18<br>25<br>18 | Death<br>Edema, pulmonary<br>Hemorrhage, pulmonary<br>Myocardial infarction, *non-Q-wave | None   | Death      |
| 006-034 6982            | 81 F     | 25                   | Myocardial infarction, non-Q-wave                                                        | None   | Recovered  |
| 006-035 6379            | 68 M     | 22<br>12<br>16       | Myocardial infarction<br>Angina, unstable<br>Angina, unstable                            | None   | Recovered  |
| 006-035 AN 6391         | 76, M    | 8                    | Cholelithiasis                                                                           | None   | Recovered  |
| 006-035 AN 6402         | 72, M    | 29                   | Phlebitis/thrombophlebitis                                                               | None   | Continuing |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject #  | Age/ Sex | Day of Onset | Adverse Experience                   | Action      | Outcome    |
|-------------------------|----------|--------------|--------------------------------------|-------------|------------|
| <b>HEPARIN ALONE</b>    |          |              |                                      |             |            |
| <b>PRISM-PLUS Trial</b> |          |              |                                      |             |            |
| 006-036 6185            | 60 M     | 15           | Myocardial infarction, non-Q-wave    | None        | Recovered  |
| 006-036 6235            | 64 M     | 16           | Infection, urinary tract             | None        | Recovered  |
|                         |          | 9            | Hemorrhage, mediastinum              |             |            |
| 006-036 7089            | 56 F     | 11           | Occlusion, arterial, lower extremity | None        | Recovered  |
| 006-037 1303            | 66 M     | 12           | Death                                | None        | Recovered  |
|                         |          | 11           | Cerebrovascular accident             |             |            |
|                         |          | 12           | Cardiac arrest                       |             |            |
| 006-037 6081            | 57 F     | 18           | Anaphylaxis                          | None        | Recovered  |
| 006-037 6082            | 50 F     | 28           | Dyspnea                              | None        | Recovered  |
|                         |          | 28           | Pain, chest                          |             |            |
|                         |          | 2            | Drug overdose                        |             |            |
| 006-037 6690            | 83 M     | 4            | Bleeding, postoperative              | None        | Recovered  |
| 006-038 6093            | 77 F     | 14           | Pneumonia                            | None        | Recovered  |
| 006-040 1079            | 44 M     | 3            | Drug overdose                        | Interrupted | Recovered  |
| 006-040 1261            | 73 M     | 20           | Angina, unstable                     | None        | Recovered  |
| 006-040 6170            | 60 F     | 12           | Abscess, mediastinum                 | None        | Recovered  |
| 006-040 6801            | 74 M     | 9            | Confusion                            | None        | Recovered  |
| 006-040 6802            | 65 M     | 21           | Angina, unstable                     | None        | Recovered  |
| 006-041 1257            | 55 M     | 23           | Pain, chest                          | None        | Recovered  |
| 006-041 6026            | 56 M     | 22           | Infection, bacterial                 | None        | Recovered  |
| 006-041 6718            | 89 M     | 3            | Death                                | None        | Death      |
|                         |          | 3            | Shock, cardiogenic                   |             |            |
| 006-042 6045            | 67 M     | 1            | Drug overdose                        | None        | Recovered  |
| 006-042 6071            | 68 F     | 1            | Drug overdose                        | None        | Recovered  |
| 006-042 6354            | 75 F     | 19           | Death                                | None        | Death      |
|                         |          | 19           | Edema, pulmonary                     |             |            |
|                         |          | 8            | Infection, urinary tract             |             |            |
|                         |          | 4            | Edema, pulmonary                     |             |            |
|                         |          | 10           | Septicemia                           |             |            |
|                         |          | 4            | Hypertensive crisis                  |             |            |
| 006-042 6518            | 64 F     | 4            | Drug overdose                        | None        | Recovered  |
| 006-042 6646            | 67 M     | 22           | Angina, unstable                     | None        | Recovered  |
| 006-042 6651            | 75 M     | 13           | Renal insufficiency                  | None        | Recovered  |
|                         |          | 3            | Hepatic insufficiency                |             |            |
|                         |          | 22           | Cerebrovascular accident             |             |            |
|                         |          | 8            | Neoplasm, prostate                   |             | Continuing |
| 006-042 6854            | 42 F     | 1            | Drug overdose                        | None        | Recovered  |
| 006-042 6861            | 68 F     | 5            | Cardiac arrest                       | None        | Death      |
|                         |          | 5            | Death                                |             |            |
| 006-042 6963            | 80 F     | 4            | Bleeding, postoperative              | None        | Recovered  |
| 006-042 6995            | 53 F     | 4            | AV block, third degree               | None        | Recovered  |
| 006-043 6366            | 81 M     | 9            | Death                                | None        | Death      |
|                         |          | 9            | Ventricular tachycardia              |             |            |
|                         |          | 9            | Cardiac arrest                       |             |            |
| 006-043 6676            | 85 M     | 18           | Death                                | None        | Death      |
|                         |          | 18           | Shock                                |             |            |
|                         |          | 18           | Hemorrhage, retroperitoneal          |             |            |
| 006-043 6681            | 69 M     | 25           | Pain, abdominal                      | None        | Recovered  |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject #  | Age/ Sex | Day of Onset                     | adverse Experience                                                                                                                       | Action | Outcome   |
|-------------------------|----------|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|--------|-----------|
| <b>HEPARIN ALONE</b>    |          |                                  |                                                                                                                                          |        |           |
| <b>PRISM-PLUS Trial</b> |          |                                  |                                                                                                                                          |        |           |
| 006-044 1046            | 78 M     | 19<br>15                         | Ventricular fibrillation<br>Pseudoaneurysm                                                                                               | None   | Recovered |
| 006-044 1067            | 86 F     | 27<br>25<br>25<br>24<br>26<br>25 | Death<br>Edema, pulmonary<br>Respiratory failure<br>Shock, cardiogenic<br>Fracture, knee<br>Anemia<br>Myocardial infarction              | None   | Death     |
| 006-044 1125            | 65 M     | 26                               | Infection, wound                                                                                                                         | None   | Recovered |
| 006-044 1688            | 46 M     | 21                               | Pericarditis                                                                                                                             | None   | Recovered |
| 006-044 6126            | 59 M     | 16<br>16                         | Death<br>Left ventricular hypertrophy                                                                                                    | None   | Death     |
| 006-044 6155            | 72 F     | 12<br>12<br>12                   | Death<br>Bleeding, postoperative<br>Dissection, aortic                                                                                   | None   | Death     |
| 006-044 6190            | 50 M     | 3                                | Drug overdose                                                                                                                            | None   | Recovered |
| 006-044 6218            | 74 M     | 1                                | Drug overdose                                                                                                                            | None   | Recovered |
| 006-044 6248            | 69 M     | 12                               | AV block, third degree                                                                                                                   | None   | Recovered |
| 006-0446747             | 51 M     | 14<br>14                         | Death<br>Sudden cardiac death                                                                                                            | None   | Death     |
| 006-044 6748            | 71 M     |                                  | Drug overdose                                                                                                                            | None   | Recovered |
| 006-044 6754            | 70 M     |                                  | Hypotension                                                                                                                              | None   | Recovered |
| 006-044 6818            | 74 F     | 21<br>21<br>21<br>21             | Death<br>Thrombocytopenia<br>Embolism/infarction, pulmonary<br>Disseminated intravascular<br>coagulopathy                                | None   | Death     |
| 006-044 6840            | 77 F     | 1                                | Drug overdose                                                                                                                            | None   | Recovered |
| 006-044 7018            | 76 F     | 17                               | Phlebitis/thrombophlebitis                                                                                                               | None   | Recovered |
| 006-044 7062            | 59 M     | 10<br>10<br>17<br>15             | Hypotension<br>Ventricular fibrillation<br>Cerebrovascular accident<br>Occlusion, arterial, lower extremity                              | None   | Recovered |
| 006-044 <b>7079</b>     | 78 M     | 2<br>1<br>2<br>2<br>2<br>2<br>2  | Death<br>Edema, pulmonary<br>Atrial fibrillation<br>Ventricular tachycardia<br>AV block, second degree<br>Shock, cardiogenic<br>Asystole | None   | Death     |
| 006-045 1654            | 74 F     | 13<br>13                         | Death<br>Hypotension                                                                                                                     | None   | Death     |
| 006-045 1658            | 85 M     | 7<br>7<br>7<br>7                 | Death<br>Ventricular fibrillation<br>Shock, cardiogenic<br>Asystole                                                                      | None   | Death     |
| 006-045 6305            | 47 M     | 13                               | Pharyngitis                                                                                                                              | None   | Recovered |
| 006-045 6660            | 80 F     | 7<br>11<br>21<br>10              | Pneumonia<br>Renal insufficiency<br>Anemia<br>Heart failure                                                                              |        |           |

15.0.3 Subjects in Heparin 'Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject #  | Age/ Sex | Day of Onset | Adverse Experience                    | Action      | Outcome              |
|-------------------------|----------|--------------|---------------------------------------|-------------|----------------------|
| <b>HEPARIN ALONE</b>    |          |              |                                       |             |                      |
| <i>PRISM-PLUS Trial</i> |          |              |                                       |             |                      |
| 006-045 6662            | 60 F     | 4            | Chronic obstructive pulmonary disease | None        | Recovered            |
| 006-045 6868            | 63 M     | 19           | Angina, unstable                      | None        | Recovered            |
| 006-046 1115            | 59 F     | 4            | Ventricular fibrillation              | None        | Recovered            |
| 006-046 1332            | 48 M     | 6            | Colic, renal                          | None        | Recovered            |
| 006-046 6159            | 61 F     | 3            | Respiratory failure                   | None        | Recovered            |
|                         |          | 3            | Chronic obstructive pulmonary disease |             |                      |
| 006-046 6809            | 64 M     | 1            | Drug overdose                         | None        | Recovered            |
| 006-046 7066            | 49 M     | 4            | Ventricular fibrillation              | None        | Recovered            |
|                         |          | 4            | Shock, cardiogenic                    |             |                      |
|                         |          | 4            | Cardiovascular hemodynamics abnormal  |             |                      |
|                         |          | 4            | Bleeding, postoperative               |             |                      |
| 006-047 5153            | 83 M     | 4            | Embolism, air                         | None        | Recovered            |
| 006-047 5178            | 82 M     | 10           | Angina, unstable                      | None        | Recovered            |
| 006-047 5356            | 60 M     | 30           | Edema, pulmonary                      | None        | Recovered            |
|                         |          | 30           | Myocardial infarction, non-Q-wave     |             |                      |
| 006-047 5519            | 72 F     | 14           | Angina pectoris                       | None        | Recovered            |
| 006-048 1169            | 56 M     | 26           | Myocardial infarction                 | None        | Continuing Recovered |
|                         |          | 3            | Confusion                             |             |                      |
| 006-048 643 1           | 71 M     | 32           | Death                                 | None        | Death                |
|                         |          | 24           | Heart failure                         |             |                      |
| 006-048 7242            | 78 F     | 5            | Death                                 | None        | Death                |
|                         |          | 5            | Cardiovascular hemodynamics abnormal  |             |                      |
|                         |          | 2            | Angina, unstable                      |             |                      |
| 006-048 7248            | 77 M     | 4            | Death                                 | None        | Death                |
| 006-049 6506            | 80 F     | 3            | Drug overdose                         | None        | Recovered            |
|                         |          | 3            | Shock, cardiogenic                    |             |                      |
| 006-049 6586            | 72 M     | 25           | Myocardial infarction                 | None        | Recovered            |
| 006-049 6590            | 73 M     | 14           | Ileus                                 | None        | Recovered            |
| 006-049 6881            | 73 M     | 26           | Angina, unstable                      | None        | Recovered            |
| 006-050 1036            | 43 F     | 4            | Allergy                               | None        | Recovered            |
| 006-050 1624            | 57 M     | 5            | Ventricular fibrillation              | None        | Recovered            |
| 006-050 1627            | 57 M     | 1            | Drug overdose                         | Interrupted | Recovered            |
| 006-050 6107            | 69 M     | 10           | Hemorrhage                            | None        | Recovered            |
| 006-050 63 10           | 78 M     | 3            | Fever                                 | None        | Recovered            |
| 006-050 6696            | 92 M     | 23           | Death                                 | None        | Death                |
|                         |          | 5            | Edema, pulmonary                      |             |                      |
|                         |          | 8            | Atrial fibrillation                   |             |                      |
|                         |          | 5            | Shock, cardiogenic                    |             |                      |
|                         |          | 5            | Renal insufficiency                   |             |                      |
| 006-050 6702            | 53 M     | 11           | Pain, chest                           | None        | Recovered            |
|                         |          | 5            | Bleeding, postoperative               |             |                      |
| 006-050 6977            | 57 F     | 16           | Infection, wound, postoperative       | None        | Recovered            |
|                         |          | 11           | Pseudoaneurysm                        |             |                      |
|                         |          | 4            | Hematoma                              |             |                      |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject #  | Age/ Sex | Day of Onset | Adverse Experience                   | Action | Outcome    |
|-------------------------|----------|--------------|--------------------------------------|--------|------------|
| <b>HEPARIN ALONE</b>    |          |              |                                      |        |            |
| <b>PRISM-PLUS Trial</b> |          |              |                                      |        |            |
| 006-053 5107            | 70 F     | 20           | Angina, unstable                     | None   | Recovered  |
| 006-053 5164            | 74 M     | 26           | Renal insufficiency                  | None   | Recovered  |
|                         |          | 26           | Pneumothorax                         |        |            |
|                         |          | 9            | Cerebrovascular accident             |        |            |
| 006-053 5293            | 68 F     | 74           | Death                                | None   | Death      |
|                         |          | 20           | Cholecystitis                        |        |            |
|                         |          | 20           | Pancreatitis                         |        |            |
|                         |          | 21           | Septicemia                           |        |            |
| 006-053 5342            | 67 M     | 8            | Diverticulum, intestinal             | None   | Recovered  |
| 006-053 5432            | 49 F     | 5            | Diplopia                             | None   | Recovered  |
| 006-053 5524            | 80 M     | 10           | Pain, chest                          | None   | Recovered  |
| 006-053 5592            | 80 M     | 14           | Bleeding, postoperative              | None   | Recovered  |
| 006-054 6703            | 58 F     | 18           | Rash                                 | None   | Recovered  |
|                         |          | 5            | Infection, infused vein              |        |            |
| 00-054 6708             | 61 M     | 12           | Myocardial infarction                | None   | Recovered  |
| 006-054 6739            | 55 F     | 6            | Hematoma                             | None   | Recovered  |
| 006-054 6744            | 68 F     | 2            | Edema, pulmonary                     | D/C'd  | Recovered  |
| 006-056 7213            | 73 F     | 17           | Angina, unstable                     | None   | Recovered  |
| 006-056 7218            | 66 M     | 14           | Mediastinitis                        | None   | Recovered  |
| 006-057 1643            | 64 F     | 5            | Cholelithiasis                       | None   | Recovered  |
| 006-057 6110            | 75 M     | 4            | Bleeding, postoperative              | None   | Recovered  |
| 006-057 6113            | 63 F     | 7            | Bleeding, postoperative              | None   | Recovered  |
| 006-057 6334            | 54 M     | 31           | Pain, chest                          | None   | Recovered  |
| 006-057 6562            | 70 F     | 4            | Bleeding, postoperative              | None   | Recovered  |
| 006-058 6429            | 62 M     | 1            | Thrombocytopenia                     | D/C'd  | Recovered  |
| 006-058 7394            | 70 M     | 9            | Occlusion, arterial, lower extremity | None   | Recovered  |
| 006-059 6326            | 72 F     | 7            | Death                                | None   | Recovered  |
|                         |          | 6            | Shock, cardiogenic                   |        |            |
| 006-059 6330            | 76 F     | 4            | Drug overdose                        | None   | Recovered  |
| 006-060 6728            | 73 M     | 4            | Cardiac arrest                       | None   | Death      |
|                         |          | 4            | Death                                |        |            |
| 006-062 1014            | 71 F     | 13           | Heart failure                        | None   | Recovered  |
| 006-062 7002            | 45 M     | 17           | Phlebitis/thrombophlebitis           | None   | Recovered  |
|                         |          | 10           | Minutes Atrial fibrillation          |        |            |
|                         |          |              | Drug overdose                        |        |            |
| 006-064 6355            | 74 F     | 1            | Hyperthermia                         | None   | Recovered  |
| 006-067 5289            | 40 M     | 2            | Drug overdose                        | None   | Recovered  |
| 006-067 5310            | 73 F     | 15           | Death                                | None   | Death      |
|                         |          | 10           | Embolism/infarction, pulmonary       |        |            |
| 006-078 1164            | 53 M     | 1            | Drug overdose                        | None   | Recovered  |
| 006-078 1700            | 83 M     | 1            | Drug overdose                        | None   | Recovered  |
| 006-079 1380            | 72 M     | 5            | Ventricular fibrillation             | None   | Recovered  |
|                         |          | 6            | Ventricular tachycardia              |        |            |
| 006-079 1382            | 68 M     | 22           | Angina, unstable                     | None   | Continuing |
| 006-079 7280            | 66 F     | 4            | Ventricular tachycardia              | None   | Recovered  |
| 006-080 7501            | 55 M     | 19           | Pneumonia                            | None   | Recovered  |
| 006-080 7721            | 70 M     | 3            | Pneumonia                            | None   | Recovered  |
| 006-080 7725            | 60 M     | 5            | Myocardial infarction, non-Q-wave    | None   | Recovered  |
| 006-084 1234            | 69 M     | 4            | Death                                |        |            |
|                         |          | 3            | Aneurysm, aortic                     |        |            |
| 006-084 7535            | 69 F     | 7            | Respiratory failure                  | None   | Recovered  |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject #  | Age/ Sex                         | Day of Onset | Adverse Experience                | Action        | Outcome   |
|-------------------------|----------------------------------|--------------|-----------------------------------|---------------|-----------|
| <b>HEPARIN ALONE</b>    |                                  |              |                                   |               |           |
| <i>PRISM-PLUS Trial</i> |                                  |              |                                   |               |           |
| 006-084 7542            | 69 F                             | 7            | Ventricular fibrillation          | None          | Recovered |
| 006-084 7651            | 71 F                             | 27           | Atrial fibrillation               | None          | Recovered |
| 006-084 7659            | 44 M                             | 8            | Angina, unstable                  | None          | Recovered |
|                         |                                  | 26           | Angina, unstable                  |               |           |
|                         |                                  | 29           | Angina, unstable                  |               |           |
| 006-084 7802            | 56 F                             | 33<br>6      | Death<br>Days Heart failure       | None          | Recovered |
| 006-084 7804            | 75 M                             | 5<br>5       | Death<br>Ventricular fibrillation | None          | Recovered |
| 006-085 7566            | 52 F                             | 6            | Angina, unstable                  | None          | Recovered |
| 006-086 122             | 75 F                             | 1            | Ventricular fibrillation          | None          | Recovered |
| 006-087 7519            | 59 M                             | 1            | Drug overdose                     | None          | Recovered |
| 006-089 1541            | 65 M                             | 10           | Death                             | None<br>D/C'd | Death     |
|                         |                                  | 3            | Shock, cardiogenic                |               |           |
| 006-089 7631            | 46 M                             | 3            | Death                             | None<br>D/C'd | Death     |
|                         |                                  | 3            | Shock, cardiogenic                |               |           |
| 006-091 7423            | 68 M                             | 14           | Death                             | None          | Death     |
|                         |                                  | 5            | Renal insufficiency               |               |           |
|                         |                                  | 8            | Respiratory failure               |               |           |
|                         |                                  | 9            | Encephalopathy, metabolic         |               |           |
|                         |                                  | 13           | Shock                             |               |           |
| 2                       | Cardiovascular hemodynamics abnl | D/C'd        |                                   |               |           |
| 006-092 7418            | 56 M                             | 12           | Death                             | None          | Death     |
|                         |                                  | 7            | Renal insufficiency               |               |           |
|                         |                                  | 7            | Pneumonia                         |               |           |
|                         |                                  | 10           | Shock, septic                     |               |           |
| 006-093 1203            | 65 F                             | 20           | Angina, unstable                  | None          | Recovered |
| 006-093 7439            | 89 F                             | 2            | Edema, cerebral                   | D/C'd         | REcovered |
| 006-093 7457            | 79 F                             | 22           | Death                             | None          | Death     |
|                         |                                  | 12           | Pneumonia                         |               |           |
|                         |                                  | 12           | Respiratory insufficiency         |               |           |
| 006-094 7613            | 68 F                             | 7            | Death                             | None          | Death     |
|                         |                                  | 7            | Dissection, coronary              |               |           |
| 006-094 7713            | 80 F                             | 4            | Heart failure                     | None          | Recovered |
| 006-094 7742            | 60 M                             | 2            | Death                             | D/C'd         | Death     |
|                         |                                  | 2            | Cardiac arrest                    |               |           |
| 006-094 7744            | 69 M                             | 1            | Drug overdose                     | None          | Recovered |
| 006-095 1184            | 74 M                             | 24           | Myocardial infarction             | None          | Recovered |
|                         |                                  | 4            | Ventricular fibrillation          |               |           |
| 006-095 1566            | 63 M                             | 7            | Death                             | None          | Death     |
|                         |                                  | Death        | Cardiac arrest                    |               |           |
| 006-095 7638            | 74 M                             | 13           | Death                             | None          | Death     |
|                         |                                  | 12           | Shock, cardiogenic                |               |           |
|                         |                                  | 9            | Infection, bacterial Severe       |               |           |
| 006-102 5502            | 73 F                             | 7            | Pain, neck                        | None          | Recovered |
|                         |                                  | 7            | Pain, shoulder                    |               |           |
| 006-106 5462            | 64 M                             | 14           | Pain, chest                       | None          | Recovered |
| 006-108 7847            | 55 M                             | 4            | Ventricular fibrillation          |               |           |
| 006-108 7857            | 80 F                             | 10           | Death                             | None          | Death     |
|                         |                                  | 6            | Respiratory failure               |               |           |
|                         |                                  | 6            | Shock, cardiogenic                |               |           |
|                         |                                  | 10           | Asystole                          |               |           |
|                         |                                  | 6            | Bronchitis, chronic               |               |           |

150.3 Subjects in Heparin' Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject # | Age/ Sex | Day of Onset      | Adverse Experience                                                                                   | Action | Outcome    |
|------------------------|----------|-------------------|------------------------------------------------------------------------------------------------------|--------|------------|
| IEPARIN ALONE          |          |                   |                                                                                                      |        |            |
| <b>RISM Trial</b>      |          |                   |                                                                                                      |        |            |
| 11-001 1813            | 40 M     | 15<br>27          | Asthenia/fatigue<br>Infection, skin                                                                  | None   | Recovered  |
| 11-001 1836            | 93 F     | 2                 | Pain, abdominal                                                                                      | None   | Recovered  |
| 11-002 1047            | 72 M     | 18<br>5<br>7<br>9 | Heart failure<br>Renal insufficiency<br>Disorientation<br>Tremor                                     | None   | Recovered  |
| 11-004 1116            | 56 M     | 1                 | Drug overdose                                                                                        | None   | Recovered  |
| 11-004 1445            | 67 M     | 23                | Pain, abdominal                                                                                      | None   | Recovered  |
| 11-004 2352 71         | 71 M     | 4<br>4            | Thrombocytopenia<br>Bleeding, postoperative                                                          | None   | Recovered  |
| 11-005 1917            | 74 M     | 19<br>24          | Heart failure<br>Infection, urinary tract                                                            | None   | Recovered  |
| 11-007 1457            | 76 M     | 17<br>2           | Pain, chest<br>Drug overdose                                                                         | None   | Recovered  |
| 11-007 2055            | 57 F     | 15<br>23<br>23    | Angina, unstable<br>Angina, unstable<br>Heart failure                                                | None   | Recovered  |
| 11-008 2188            | 58 M     | 3                 | Dissection, coronary artery                                                                          | None   | Recovered  |
| 11-008 2284            | 85 M     | 8                 | Bleeding, postoperative                                                                              | None   | Recovered  |
| 11-011 1056            | 84 F     | 24<br>21<br>25    | Respiratory failure<br>Angina, unstable<br>Myocardial infarction, non-Q-wave                         | None   | Recovered  |
| 11-011 1058            | 55 M     | 1                 | Drug overdose                                                                                        | None   | Recovered  |
| D11-011 1141           | 47 M     | 8                 | Hemorrhage Severe                                                                                    | None   | Recovered  |
| D11-011 1143           | 54 F     | 15<br>2<br>14     | Effusion, pleural<br>Drug overdose<br>Infection, postoperative                                       | None   | Recovered  |
| 011-011 1455           | 58 M     | 20                | Heart failure                                                                                        | None   | Recovered  |
| 011-011 1801           | 58 M     | 1<br>2<br>3<br>20 | Thrombocytopenia<br>Bleeding, postoperative<br>Electromechanical dissociation<br>Atrial fibrillation | None   | Recovered  |
| 011-013 1195           | 72 M     | 10                | Transient ischemic attack                                                                            | None   | Recovered  |
| 011-013 1277           | 65 M     | 2<br>23           | Confusion<br>Confusion                                                                               | None   | Recovered  |
| 011-013 2141           | 67 M     | 24                | Heart failure                                                                                        | None   | Recovered  |
| 011-013 2142           | 76 M     | 17                | Chronic obstructive pulmonary disease                                                                | None   | Continuing |
| 011-016 1147           | 72 F     | 2<br>10<br>8      | Tachycardia-bradycardia syndrome<br>Pneumothorax<br>Cardiovascular hemodynamics<br>Abnormal          | None   | Recovered  |
| 011-016 1224           | 43 M     | 16<br>16<br>16    | Myocardial infarction<br>Hypotension<br>Hypoxemia                                                    | None   | Recovered  |
| 011-016 1243           | 60 M     | 26<br>31          | Angina pectoris<br>Angina pectoris                                                                   | None   | Recovered  |
| 011-016 1860           | 54 M     | 9                 | Cardiac arrest                                                                                       | None   | Recovered  |
| 011-016 1863           | 58 M     | 27                | Fever                                                                                                | None   | Recovered  |
| 011-016 1868           | 65 F     | 27                | Cellulitis                                                                                           | None   | Recovered  |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject # | Age/ Sex           | Day of Onset | Adverse Experience                  | Action | Outcome    |
|------------------------|--------------------|--------------|-------------------------------------|--------|------------|
| <b>IEPARIN ALONE</b>   |                    |              |                                     |        |            |
| <b>RISM Trial</b>      |                    |              |                                     |        |            |
| 11-021 1067            | 70 M               | 4            | Surgery, heart vessel, complication | None   | Recovered  |
| 11-021 1072            | 67 M               | 1            | Drug overdose                       | None   | Recovered  |
| 11-021 1205            | 71 M               | 7            | Cardiac arrest                      | None   | Recovered  |
| 11-021 1230            | 79 F               | 5            | Panic disorder                      | None   | Recovered  |
| 11-021 1232            | 66 F               | 43           | Death                               | None   | Death      |
|                        |                    | 30           | Heart failure                       |        |            |
|                        |                    | 19           | Embolism/infarction, pulmonary      |        |            |
| 11-021 1237            | 57 F               | 7            | Angina, unstable                    | None   | Recovered  |
| 11-021 1713            | 71 M               | 7            | CVA                                 | None   | Recovered  |
| 11-021 1721            | 68 M               | 4            | Moderate                            | None   | Recovered  |
| 11-021 1723            | 68 M               | 16           | Angina, unstable                    | None   | Recovered  |
| 11-021 2125            | 75 M               | 2            | Hematuria                           | None   | Recovered  |
| 11-021 2129            | 74 F               | 20           | Angina, unstable                    | None   | Recovered  |
| 11-021 2135            | 73 M               | 16           | Renal insufficiency                 | None   | Recovered  |
|                        |                    | 9            | Respiratory failure                 |        |            |
|                        |                    | 12           | Respiratory failure                 |        |            |
|                        |                    | 13           | Respiratory failure                 |        |            |
|                        |                    | 21           | Respiratory failure                 |        |            |
|                        |                    | 29           | Respiratory failure                 |        |            |
|                        |                    | 33           | Respiratory failure                 |        |            |
| 9                      | Cardiac output low |              |                                     |        |            |
| 11-021 2504            | 91 M               | 17           | Death                               | None   | Death      |
|                        |                    | 17           | Myocardial infarction               |        |            |
| 11-023 1685            | 64 M               | 18           | Angina, unstable                    | None   | Recovered  |
| 11-024 1771            | 67 F               | 1            | Drug overdose                       | None   | Recovered  |
| 11-024 1772            | 70 M               | 18           | Pain, chest                         | None   | Recovered  |
|                        |                    | 18           | Heart failure                       |        |            |
| 11-026 1001            | 70 M               | 12           | Angina pectoris                     | None   | Recovered  |
| 11-026 1006            | 62 M               | 3            | Angina, unstable                    | None   | Recovered  |
| 11-026 1420            | 52 M               | 8            | Respiratory distress                | None   | Recovered  |
|                        |                    | 17           | Cholelithiasis                      |        |            |
| 11-032 1350            | 66 F               | 25           | Angina, unstable                    | None   | Recovered  |
| 11-032 1357            | 74 M               | 2            | Parkinsonism worsening              | None   | Continuing |
| 11-032 1359            | 69 M               | 3            | Fever                               | None   | Recovered  |
| 11-032 1785            | 59 M               | 7            | CVA                                 | None   | Recovered  |
| 11-032 2434            | 63 F               | 27           | Angina, unstable                    | None   | Recovered  |
| 11-033 1026            | 54 M               | 2            | Drug overdose                       | None   | Recovered  |
| 11-042 1652            | 45 M               | 1            | Drug overdose                       | None   | Recovered  |
| 11-043 1465            | 70 M               | 5            | Angina pectoris                     | None   | Recovered  |
| 11-044 3353            | 53 M               | 55           | Death                               | None   | Death      |
|                        |                    | 7            | Brain damage, anoxic                |        |            |
| 11-044 3358            | 75 F               | 30           | Death                               | None   | Death      |
|                        |                    | 30           | Cardiac arrest                      |        |            |
|                        |                    | 18           | Pain, chest                         |        |            |
|                        |                    | 18           | Syncope                             |        |            |
|                        |                    | 18           | Middle ear disorder                 |        |            |
| 11-045 3383            | 78 F               | 1            | Drug overdose                       | None   | Recovered  |
| 11-045 3686            | 51 M               | 12           | Death                               | None   | Death      |
|                        |                    | 12           | Arrhythmia                          |        |            |
|                        |                    | 12           | Myocardial infarction               |        |            |
| 11-047 1953            | 76 M               | 11           | AV block, third degree              | None   | Recovered  |

150.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject # | Age/ Sex | Day of Onset          | Adverse Experience                                                                            | Action | Outcome    |
|------------------------|----------|-----------------------|-----------------------------------------------------------------------------------------------|--------|------------|
| <b>HEPARIN ALONE</b>   |          |                       |                                                                                               |        |            |
| <b>PRISM Trial</b>     |          |                       |                                                                                               |        |            |
| 01 I-048 13x.5         | 68 F     | 1 2                   | Edema pulmonary                                                                               | None   | Recovered  |
| 01 I-050 2100          | 77 M     | 23                    | Infection, wound                                                                              | None   | Recovered  |
| 011-050 2103           | 59 M     | 24                    | Infection, wound                                                                              | None   | Recovered  |
| 01 I-054 1701          | 74 M     | 4<br>4<br>4           | Death<br>Cardiac arrest<br>Hypotension                                                        | None   | Death      |
| 011-054 1708           | 69 M     | 22                    | Angina pectoris                                                                               | None   | Recovered  |
| 011-054 1712           | 62 M     | 19                    | Pain, chest                                                                                   | None   | Recovered  |
| 011-054 2275           | 69 M     | 13<br>18              | Angina, unstable<br>Angina, unstable                                                          | None   | Recovered  |
| 01 I-057 1074          | 64 M     | 4<br>3                | Cardiac arrest<br>Ventricular fibrillation                                                    | None   | Recovered  |
| 01 I-058 1662          | 54 M     | 14                    | Myocardial infarction                                                                         | None   | Recovered  |
| 01 I-058 2172          | 58 F     | 12                    | Pneumonia, bacterial                                                                          | None   | Recovered  |
| 01 I-059 4028          | 52 F     | 28<br>16              | Thrombosis, deep vein<br>Angina pectoris                                                      | None   | Recovered  |
| 01 I-059 4620          | 73 F     | 14                    | Angina, unstable                                                                              | None   | Recovered  |
| 01 I-060 4015          | 51 M     | 3<br>3<br>3           | Death<br>Respiratory failure<br>Shock, cardiogenic                                            | None   | Death      |
| 01 I-060 4033          | 71 M     | 10                    | Angina pectoris                                                                               | None   | Recovered  |
| 011-060 4041           | 65 M     | 72<br>11<br>71<br>11  | Death<br>Coma<br>Respiratory failure<br>CVA                                                   | None   | Death      |
| 01 I-060 4606          | 59 F     | 15                    | Myocardial infarction                                                                         | None   | Recovered  |
| 011-061 2874           | 44 M     | 13                    | Pericarditis                                                                                  | None   | Recovered  |
| 011-061 2876           | 78 M     | 4<br>1<br>2           | Death<br>Edema, pulmonary<br>Shock, cardiogenic                                               | None   | Death      |
| 011-061 3091           | 89 F     | 27<br>18              | Death<br>CVA                                                                                  | None   | Death      |
| 01 I-061 3099          | 74 F     | 4                     | Infection, injection site                                                                     | None   | Recovered  |
| 01 I-061 3621          | 62 F     | 26                    | Infection, wound                                                                              | None   | Recovered  |
| 011-061 4972           | 67 M     | 7<br>6<br>4           | Death<br>Hematoma<br>CVA                                                                      | None   | Death      |
| 01 I-061 5160          | 79 F     | 9<br>8<br>9<br>8<br>7 | Death<br>Hypotension<br>Vascular insufficiency, intestinal<br>Shock, septic<br>Pseudoaneurysm | None   | Death      |
| 011-061 5165           | 60 M     | 29                    | Cellulitis                                                                                    | None   | Recovered  |
| 011-061 5421           | 65 M     | 4                     | Hypotension                                                                                   | None   | Recovered  |
| 011-061 5423           | 71 M     | 6                     | Cholecystitis                                                                                 | None   | Recovered  |
| 011-061 5426           | 59 M     | 13                    | Angina, unstable                                                                              | None   | Recovered  |
| 011-061 7453           | 64 M     | 14                    | Ulcer, peptic                                                                                 | None   | Continuing |
| 011-061 7459           | 67 M     | 15<br>1               | Angina, unstable<br>Drug overdose                                                             | None   | Recovered  |
| 011-061 7547           | 59 M     | 25                    | Palpitation                                                                                   | None   | Recovered  |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/ Subject #  | Age/ Sex | Day of Onset          | Adverse Experience                                                                                              | Action | Outcome    |
|----------------------|----------|-----------------------|-----------------------------------------------------------------------------------------------------------------|--------|------------|
| <b>HEPARIN ALONE</b> |          |                       |                                                                                                                 |        |            |
| <i>PRISM Trial</i>   |          |                       |                                                                                                                 |        |            |
| 011-061 7551         | 52 M     | 3                     | Drug overdose                                                                                                   | None   | Recovered  |
| 011-061 7556         | 50 M     | 26                    | Angina, unstable                                                                                                | None   | Recovered  |
| 011-062 3335         | 68 M     | 3<br>3<br>3<br>3<br>3 | Death<br>Occlusion, coronary artery<br>Shock, cardiogenic<br>Edema, pulmonary<br>Electromechanical dissociation | None   | Death      |
| 011-062 5109         | 63 M     | 2                     | Ulcer, gastric                                                                                                  | D/C'd  | Recovered  |
| 011-063 3930         | 44 M     | 10                    | Angina pectoris                                                                                                 | None   | Recovered  |
| 011-063 3938         | 46 M     | 25                    | Angina, unstable                                                                                                | None   | Recovered  |
| 011-063 3955         | 62 M     | 1                     | Syncope                                                                                                         | None   | Recovered  |
| 011-064 3609         | 69 M     | 9<br>2                | Heart failure<br>Drug overdose                                                                                  | None   | Recovered  |
| 011-064 3610         | 72 M     | 1                     | Drug overdose                                                                                                   | None   | Recovered  |
| 011-064 3616         | 58 F     | 3                     | Asystole                                                                                                        | None   | Recovered  |
| 011-064 4956         | 57 M     | 16<br>16<br>16<br>16  | Death<br>Hypotension<br>Ventricular fibrillation<br>Asystole                                                    | None   | Death      |
| 011-065 3277         | 71 F     | 15<br>15<br>4<br>4    | Death<br>Ventricular fibrillation<br>Shock, cardiogenic<br>Edema, pulmonary                                     | None   | Death      |
| 011-065 3280         | 50 M     | 16<br>16              | Death<br>CVA, hemorrhagic                                                                                       | None   | Death      |
| 011-065 3524         | 67 M     | 15<br>15              | Death<br>Arrhythmia                                                                                             | None   | Death      |
| 011-065 3893         | 61 F     | 6<br>4<br>4<br>3      | Death<br>Cardiac arrest<br>Shock, cardiogenic<br>Occlusion, coronary artery                                     | None   | Death      |
| 011-065 4930         | 66 M     | 12<br>12<br>12<br>12  | Death<br>Occlusion, coronary artery<br>Shock, cardiogenic<br>Electromechanical dissociation                     | None   | Death      |
| 011-066 2909         | 47 M     | 11                    | Angina, unstable                                                                                                | None   | Recovered  |
| 011-066 2912         | 55 M     | 6                     | Hypothyroidism                                                                                                  | None   | Recovered  |
| 011-066 2914         | 57 F     | 23                    | Myocardial infarction                                                                                           | None   | Recovered  |
| 011-066 3101         | 83 F     | 5                     | Pneumonia                                                                                                       | None   | Recovered  |
| 011-066 3102         | 83 M     | 6<br>5<br>3<br>5      | Death<br>Hypotension<br>Pneumonia<br>Edema, pulmonary                                                           | None   | Death      |
| 011-066 3292         | 78 F     | 2                     | Bronchitis                                                                                                      | None   | Recovered  |
| 011-066 3733         | 64 F     | 12                    | Pain, chest                                                                                                     | None   | Recovered  |
| 011-066 3738         | 71 F     | 13                    | Angina, unstable                                                                                                | None   | Recovered  |
| 011-069 4294         | 72 F     | 1                     | Embolism/infarction, pulmonary                                                                                  | None   | Recovered  |
| 011-070 6564         | 61 M     | 27                    | Angina, unstable                                                                                                | None   | Recovered  |
| 011-070 6731         | 71 M     | 27                    | Angina, unstable                                                                                                | None   | Continuing |
| 011-070 6736         | 61 M     | 5<br>5<br>5           | Death<br>Cardiac arrest<br>Shock, cardiogenic                                                                   | None   | Death      |
| 011-071 4349         | 48 M     | 22                    | Atrial fibrillation                                                                                             | None   | Recovered  |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject # | Age/ Sex | Day of Onset   | Adverse Experience                                                 | Action | Outcome   |
|------------------------|----------|----------------|--------------------------------------------------------------------|--------|-----------|
| <b>HEPARIN ALONE</b>   |          |                |                                                                    |        |           |
| <i>PRISM Trial</i>     |          |                |                                                                    |        |           |
| 011-071 6571           | 60 M     | 4              | Shock, cardiogenic                                                 | None   | Recovered |
| 011-072 4320           | 65 M     | 7              | Pseudoaneurysm                                                     | None   | Recovered |
| 011-072 4323           | 75 M     | 14             | Infection, wound                                                   | None   | Recovered |
| 011-072 4337           | 65 M     | 4              | Infection, respiratory                                             | None   | Recovered |
| 011-072 4425           | 77 F     | 6              | Death                                                              | None   | Death     |
| 011-072 6605           | 72 M     | 14<br>22       | Angina, unstable<br>Angina, unstable                               | None   | Recovered |
| 011-072 6745           | 49 M     | 21             | Pancreatitis                                                       |        |           |
| 011-072 6748           | 62 F     | 8<br>25        | Angina, unstable<br>Infection, wound, postoperative                | None   | Recovered |
| 011-072 6810           | 83 M     | 1<br>1<br>1    | Death<br>Heart failure<br>Shock, cardiogenic                       | D/C'd  | Death     |
| 011-072 6813           | 64 F     | 23             | Angina, unstable                                                   | None   | Recovered |
| 011-072 7001           | 58 M     | 8<br>7         | Death<br>Anaphylaxis                                               | None   | Death     |
| 011-074 1037           | 50 F     | 1              | Drug overdose                                                      | None   | Recovered |
| 011-074 2321           | 51 M     | 5              | Hypotension                                                        | None   | Recovered |
| 011-076 3576           | 51 M     | 27             | Angina, unstable                                                   | None   | Recovered |
| 011-076 4835           | 51 M     | 6              | Angina, unstable                                                   | None   | Recovered |
| 011-077 3055           | 67 M     | 17             | Angina, unstable                                                   | None   | Recovered |
| 011-077 3706           | 47 M     | 16             | Angina, unstable                                                   | None   | Recovered |
| 011-077 5434           | 72 M     | 12             | Angina, unstable                                                   | None   | Recovered |
| 011-078 3069           | 71 F     | 23             | Angina, unstable                                                   | None   | Recovered |
| 011-079 2831           | 62 M     | 9<br>2<br>2    | Death<br>Heart failure<br>Dissection, aortic                       | None   | Death     |
| 011-079 3273           | 74 M     | 20             | Angina, unstable                                                   | None   | Recovered |
| 011-079 3504           | 73 M     | 2<br>2         | Bradycardia<br>Hypotension                                         | None   | Recovered |
| 011-079 3506           | 81 M     | 21<br>21<br>12 | Cardiac arrest<br>Respiratory insufficiency<br>Renal insufficiency | None   | Recovered |
| 011-079 3749           | 77 F     | 27             | Angina, unstable                                                   | None   | Recovered |
| 011-079 3758           | 79 M     | 6              | Phlebitis, infected                                                | None   | Recovered |
| 011-079 3853           | 78 F     | 17<br>11       | Mediastinitis<br>Infection, wound                                  | None   | Recovered |
| 011-079 5005           | 50 M     | 14             | Angina, unstable                                                   | None   | Recovered |
| 011-079 5021           | 37 M     | 11             | Angina, unstable                                                   | None   | Recovered |
| 011-079 5028           | 75 M     | 11<br>5        | Death<br>Heart failure                                             | None   | Death     |
| 011-081 6644           | 70 F     | 9              | Ulcer, gastric                                                     | None   | Recovered |
| 011-081 6667           | 71 M     | 19             | Angina, unstable                                                   |        |           |
| 011-082 2814           | 44 F     | 12             | Angina, unstable                                                   | None   | Recovered |
| 011-082 2844           | 67 M     | 3<br>3         | Death<br>Ventricular fibrillation                                  | None   | Death     |
| 011-082 2854           | 54 M     | 22<br>21<br>21 | Death<br>Myocardial infarction<br>Ventricular arrhythmia           | None   | Recovered |
| 011-082 3677           | 65 M     | 9              | Angina, unstable                                                   | None   | Recovered |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject # | Age/ Sex | Day of Onset               | Adverse Experience                                                                                                                     | Action | Outcome   |
|------------------------|----------|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------|--------|-----------|
| <b>HEPARIN ALONE</b>   |          |                            |                                                                                                                                        |        |           |
| <i>PRISM Trial</i>     |          |                            |                                                                                                                                        |        |           |
| 011-084 6383           | 74 F     | 2<br>2                     | Death<br>Edema, pulmonary                                                                                                              | D/C'd  | Death     |
| 011-085 2809           | 66 M     | 24<br>17<br>24             | Death<br>Renal insufficiency<br>CVA                                                                                                    | None   | Death     |
| 011-085 2866           | 60 F     | 24<br>24<br>17             | Death<br>Renal insufficiency<br>Septicemia                                                                                             | None   | Death     |
| 011-085 3906           | 62 M     | 14                         | Pain, abdominal                                                                                                                        | None   | Recovered |
| 011-089 2117           | 76 F     | 11<br>11<br>11             | Dyspnea<br>Rash<br>Edema/swelling                                                                                                      | None   | Recovered |
| 011-089 2118           | 57 M     | 19<br>20                   | Angina, unstable<br>Myocardial infarction                                                                                              | None   | Recovered |
| 011-089 2249           | 79 F     | 6<br>6                     | Pain, abdominal<br>Hematoma                                                                                                            | None   | Recovered |
| 011-089 2312           | 36 M     | 8                          | Pain, arm                                                                                                                              | None   | Recovered |
| 011-089 2373           | 59 F     | 6<br>6<br>6<br>7<br>6<br>6 | Cardiac arrest<br>Hypotension<br>Ventricular fibrillation<br>Thrombocytopenia<br>Bleeding, postoperative<br>Occlusion, coronary artery | None   | Recovered |
| 011-089 2375           | 53 F     | 11                         | Pain, chest                                                                                                                            | None   | Recovered |
| 011-089 2390           | 78 M     | 3<br>3                     | Death<br>Chronic obstructive pulmonary disease                                                                                         | None   | Death     |
| 011-089 7620           | 76 M     | 1                          | Drug overdose                                                                                                                          | None   | Recovered |
| 011-089 7627           | 66 M     | 18                         | Effusion, pleural                                                                                                                      | None   | Recovered |
| 011-089 7880           | 53 M     | 16                         | Arrhythmia                                                                                                                             |        |           |
| 011-092 1320           | 73 M     | 13<br>2<br>2               | Death<br>Aneurysm, aortic<br>Hemorrhage, intracranial                                                                                  | None   | Death     |
| 011-092 1372           | 74 M     | 14                         | Angina, unstable                                                                                                                       | None   | Recovered |
| 011-092 1677           | 82 M     | 2                          | CVA                                                                                                                                    | None   | Recovered |
| 011-092 1679           | 51 M     | 13                         | Gout                                                                                                                                   | None   | Recovered |
| 011-092 2467           | 71 F     | 15<br>15<br>15             | Death<br>Shock, cardiogenic<br>Cardiac tamponade                                                                                       | None   | Death     |
| 011-093 1761           | 75 F     | 13<br>12                   | Pneumonia<br>Septicemia                                                                                                                | None   | Recovered |
| 011-097 2974           | 61 M     | 2<br>2<br>1<br>2           | Pain, abdominal<br>Pain, back<br>Dyspnea<br>Atrial fibrillation                                                                        | None   | Recovered |
| 011-098 3024           | 42 F     | 17                         | Pain, chest                                                                                                                            |        |           |
| 011-098 3030           | 75 M     | 6<br>5                     | Death<br>Shock, cardiogenic                                                                                                            | None   | Death     |
| 011-098 3031           | 73 F     | 22                         | Pyelonephritis, acute                                                                                                                  | None   | Recovered |
| 011-099 3247           | 74 F     | 6                          | Cardiac arrest                                                                                                                         | None   | Recovered |
| 011-100 3001           | 58 F     | 1                          | Drug overdose                                                                                                                          | None   | Recovered |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject # | Age/ Sex | Day of Onset               | Adverse Experience                                                                                   | Action | Outcome    |
|------------------------|----------|----------------------------|------------------------------------------------------------------------------------------------------|--------|------------|
| <b>HEPARIN ALONE</b>   |          |                            |                                                                                                      |        |            |
| <b>PRISM Trial</b>     |          |                            |                                                                                                      |        |            |
| 01 I-100 3169          | 49 M     | 13                         | Anaphylaxis                                                                                          | None   | Recovered  |
| 011-103 3198           | 64 M     | 15<br>16                   | Pain, chest<br>Bronchitis                                                                            | None   | Recovered  |
| 011-103 3215           | 80 M     | 16                         | Angina, unstable                                                                                     | None   | Recovered  |
| 01 I-104 3193          | 65 M     | 23<br>23                   | Pneumonia<br>Infection, wound                                                                        | None   | Recovered  |
| 01 I-109 2355          | 42 F     | 2                          | Drug overdose                                                                                        | None   | Recovered  |
| 011-111 1259           | 68 F     | 19                         | Angina, unstable                                                                                     | None   | Recovered  |
| 01 I-1 13 6488         | 69 F     | 5                          | CVA                                                                                                  | None   | Continuing |
| 011-113 6490           | 82 M     | 6<br>6                     | Death<br>Occlusion, coronary artery                                                                  | None   | Death      |
| 011-114 3720           | 51 M     | 1                          | Drug overdose                                                                                        | None   | Recovered  |
| 011-114 3748           | 76 F     | 6                          | Occlusion, coronary artery                                                                           | None   | Recovered  |
| 011-1 14 5551          | 70 F     | 2                          | AV conduction disorder                                                                               | None   | Recovered  |
| 011-114 5661           | 85 F     | 5<br>3                     | Death<br>Respiratory distress syndrome                                                               | None   | Death      |
| 011-114 5863           | 70 M     | 23                         | Mediastinitis                                                                                        | None   | Recovered  |
| 011-115 4105           | 56 M     | 2                          | Drug overdose                                                                                        | D/C'd  | Recovered  |
| 011-116 3123           | 63 M     | 22<br>13<br>13<br>13       | Death<br>Pneumonia<br>Shock, cardiogenic<br>Shock; septic                                            | None   | Death      |
| 011-117 3779           | 60 M     | 16                         | Renal insufficiency                                                                                  | None   | Continuing |
| 011-117 3791           | 79 M     | 28<br>25<br>28             | Death<br>Myocardial infarction<br>Myocardial infarction                                              | None   | Death      |
| 011-117 4709           | 64 M     | 17                         | Angina, unstable                                                                                     | None   | Recovered  |
| 011-118 2964           | 57 M     | 3<br>3<br>3<br>3<br>2      | Death<br>Edema, pulmonary<br>Ventricular fibrillation<br>Shock, cardiogenic<br>Hemorrhage, I.V. site | D/C'd  | Death      |
| 011-119 4386           | 61 M     | 15<br>15<br>16<br>14<br>14 | Hypotension<br>Septicemia<br>Renal insufficiency, acute<br>CVA<br>Bleeding, postoperative            | None   | Recovered  |
| 01 I-1 19 6603         | 66 F     | 18                         | Angina, unstable                                                                                     | None   | Recovered  |
| 01 I-120 5293          | 45 M     | 2                          | Rales/rhonchi                                                                                        | None   | Recovered  |
| 01 I-120 5302          | 74 M     | 15<br>7                    | Death<br>Vascular insufficiency, intestinal                                                          | None   | Death      |
| 01 I-120 7517          | 72 M     | 18                         | Angina, unstable                                                                                     | None   | Recovered  |
| 011-122 3145           | 76 M     | 20                         | Angina, unstable                                                                                     | None   | Recovered  |
| 011-122 3148           | 74 F     | 26                         | Angina, unstable                                                                                     | None   | Recovered  |
| 011-122 7536           | 66 F     | 15                         | Volvulus                                                                                             | None   | Recovered  |
| 011-122 7537           | 58 F     | 13                         | Pseudoaneurysm                                                                                       | None   | Recovered  |
| 011-122 7543           | 47 F     | 30                         | Edema, pulmonary                                                                                     | None   | Recovered  |
| 011-123 4446           | 65       | 9                          | Hemorrhage, retroperitoneal                                                                          | None   | Recovered  |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject # | Age/ Sex | Day of Onset | Adverse Experience       | Action | Outcome    |
|------------------------|----------|--------------|--------------------------|--------|------------|
| <b>HEPARIN ALONE</b>   |          |              |                          |        |            |
| <i>PRISM Trial</i>     |          |              |                          |        |            |
| 011-123 4468           | 62 F     | 14           | Angina pectoris          | None   | Recovered  |
| 011-123 4649           | 65 M     | 1            | Drug overdose            | None   | Recovered  |
| 011-123 4661           | 82 M     | 7            | Death                    | None   | Death      |
|                        |          | 3            | Hypotension              |        |            |
|                        |          | 3            | Confusion                |        |            |
|                        |          | 3            | Apnea                    |        |            |
|                        |          | 4            | Shock, cardiogenic       |        |            |
|                        |          | 3            | Deterioration,-general   |        |            |
| 011-123 4669           | 55 M     | 4            | Death                    | None   | Death      |
|                        |          | 4            | Edema, pulmonary         |        |            |
|                        |          | 4            | Asystole                 |        |            |
| 011-123 4674           | 82 M     | 9            | Death                    | None   | Death      |
| 011-124 7245           | 77 M     | 19           | Death                    | None   | Death      |
|                        |          | 19           | Sudden death             |        |            |
| 011-125 4552           | 83 M     | 7            | Myocardial infarction    | None   | Recovered  |
| 011-125 4566           | 63 M     | 2            | Infection, bacterial     | None   | Recovered  |
| 011-125 4569           | 71 F     | 24           | Angina, unstable         | None   | Continuing |
| 011-125 4884           | 74 F     | 2            | Death                    | None   | Death      |
|                        |          | 2            | Tachycardia              |        |            |
|                        |          | 2            | Shock, cardiogenic       |        |            |
| 011-125 4887           | 72 M     | 3            | Edema, pulmonary         | None   | Recovered  |
|                        |          | 1            | Asystole                 |        |            |
| 011-125 5059 81        | 81 M     | 20           | Anxiety                  | None   | Recovered  |
|                        |          | 20           | Angina, unstable         |        |            |
| 011-125 5687           | 69 M     | 13           | Death                    | None   | Death      |
|                        |          | 1            | Bradycardia              |        |            |
|                        |          | 11           | Tachycardia              |        |            |
|                        |          | 12           | Tachycardia              |        |            |
|                        |          | 1            | Heart failure            |        |            |
|                        |          | 13           | Shock, cardiogenic       |        |            |
| 011-125 5694           | 78 M     | 3            | Death                    | None   | Death      |
|                        |          | 3            | Edema, pulmonary         |        |            |
| 011-125 5698           | 72 M     | 3            | CVA                      | None   | Recovered  |
| 011-125 5717           | 70 F     | 8            | Angina, unstable         | None   | Recovered  |
| 011-125 7493           | 48 M     | 12           | Angina, unstable         | None   | Recovered  |
|                        |          | 21           | Angina, unstable         |        |            |
| 011-127 4532           | 74 F     | 1            | Drug overdose            | None   | Recovered  |
| 011-127 4544           | 70 M     | 2            | Ventricular fibrillation | None   | Recovered  |
| 011-127 4556           | 73 M     | 1            | Drug overdose            | None   | Recovered  |
|                        |          | 2            | Ecchymosis               |        |            |
|                        |          | 2            | Hemorrhage, I.V. site    |        |            |
| 011-127 4902           | 71 F     | 12           | Death                    | None   | Death      |
|                        |          | 10           | CVA                      |        |            |
| 011-127 4905           | 77 F     | 4            | Death                    | None   | Death      |
| 011-127 5076           | 63 M     | 14           | Angina, unstable         | None   | Recovered  |
| 011-127 5353           | 75 F     | 20           | Angina, unstable         | None   | Recovered  |
| 011-127 5358           | 54 M     | 11           | Angina, unstable         | None   | Recovered  |
|                        |          | 23           | Angina, unstable         |        |            |
| 011-127 7469           | 61 M     | 4            |                          |        |            |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject # | Age/ Sex | Day of Onset | Adverse Experience            | Action      | Outcome    |
|------------------------|----------|--------------|-------------------------------|-------------|------------|
| <b>HEPARIN ALONE</b>   |          |              |                               |             |            |
| <i>PRISM Trial</i>     |          |              |                               |             |            |
| 011-127 7471           | 62 M     | 21           | Myocardial infarction         | None        | Recovered  |
| 011-129 3131           | 76 M     | 32           | Neoplasm, liver, malignant    | None        | Continuing |
| 011-129 3132           | 79 F     | 17           | Death                         | None        | Death      |
|                        |          | 16           | Edema, pulmonary              |             |            |
| 011-129 6524           | 68 M     | 21           | Angina, unstable              | None        | Recovered  |
|                        |          | 30           | Angina, unstable              |             |            |
|                        |          | 1            | Drug overdose                 |             |            |
| 011-132 1424           | 62 M     | 21           | Pneumonia                     | None        | Recovered  |
| 011-132 2531           | 66 M     | 11           | Pneumonia                     | None        | Recovered  |
| 011-132 7850           | 75 F     | 1            | Drug overdose                 | None        | Recovered  |
| 011-136 2013           | 64 M     | 1            | Drug overdose                 | None        | Recovered  |
| 011-136 2024           | 54 M     | 23           | Alcohol dependence            | None        | Recovered  |
|                        |          | 23           | Posttraumatic stress syndrome |             |            |
| 011-136 7668           | 49 M     | 5            | Diverticulitis, intestinal    | None        | Recovered  |
| 011-137 1749           | 82 F     | 1            | Drug overdose                 | None        | Recovered  |
| 011-138 2900           | 78 M     | 16           | Angina, unstable              | None        | Recovered  |
| 011-140 4415           | 72 M     | 14           | Angina, unstable              | None        | Continuing |
| 011-145 2028           | 74 M     | 24           | Effusion, pleural             | None        | Continuing |
| 011-148 3763           | 65 M     | 2            | Drug overdose                 | None        | Recovered  |
| 011-149 6762           | 60 M     | 5            | Death                         | None        | Death      |
| 011-149 6764           | 58 M     | 18           | Lymphadenopathy               | None        | Recovered  |
|                        |          | 18           | Infection, bacterial          |             |            |
| 011-149 6827           | 72 M     | 1            | Drug overdose                 | None        | Recovered  |
| 011-151 3841           | 54 M     | 1            | Drug overdose                 | None        | Recovered  |
| 011-151 4801           | 69 M     | 12           | Pain, chest                   | <b>None</b> | Recovered  |
|                        |          | 13           | Diarrhea Severe               |             |            |
|                        |          | 13           | Dehydration                   |             |            |
|                        |          | 12           | Dyspnea                       |             |            |
|                        |          | 1            | Drug overdose                 |             |            |
| 011-151 4802           | 56 M     | 16           | Death                         | None        | Death      |
|                        |          | 16           | Sudden cardiac death          |             |            |
|                        |          | 5            | Infection, infused vein       |             |            |
| 011-151 4985           | 70 M     | 5            | Heart Failure                 | None        | Recovered  |
| 011-152 5341           | 69 M     | 23           | Myocardial infarction         | None        | Recovered  |
| 011-152 5700           | 57 M     | 1            | Drug overdose                 | None        | Recovered  |
| 011-155 4375           | 77 F     | 11           | Death                         | None        | Death      |
|                        |          | 7            | Edema, pulmonary              |             |            |
|                        |          | 7            | Renal insufficiency           |             |            |
| 011-155 6550           | 62 M     | 1            | Drug overdose                 | None        | Recovered  |
| 011-155 6578           | 67 M     | 10           | Angina, unstable              | None        | Recovered  |
|                        |          | 23           | Angina, unstable              |             |            |
|                        |          | 31           | Angina, unstable              |             |            |
| 011-155 6581           | 73 M     | 30           | Death                         | None        | Death      |
|                        |          | 29           | Hypotension                   |             |            |
|                        |          | 20           | Pneumonia                     |             |            |
|                        |          | 24           | Renal insufficiency           |             |            |
| 011-155 6582           | 70 M     | 20           | Pain, arm                     | None        | Recovered  |
|                        |          | 20           | Pain, neck                    |             |            |
| 011-155 6703           | 63 M     | 3            | Infection, bacterial          | None        | Recovered  |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject # | Age/ Sex | Day of Onset | Adverse Experience                  | Action | Outcome   |
|------------------------|----------|--------------|-------------------------------------|--------|-----------|
| <b>HEPARIN ALONE</b>   |          |              |                                     |        |           |
| <i>RISM Trial</i>      |          |              |                                     |        |           |
| 11-155 6712            | 43 M     | 8            | Pain, chest                         | None   | Recovered |
| 11-155 6796            | 55 M     | 18           | Pain, chest                         | None   | Recovered |
|                        |          | 23           | Pain, chest                         |        |           |
| 11-155 6875            | 47 M     | 24           | Fever                               | None   | Recovered |
| 11-156 2260            | 55 F     | 1            | Hypotension                         | D/C'd  | Recovered |
|                        |          | 1            | AV block, second degree             |        |           |
| 11-156 2549            | 55 M     | 2            | Pneumonia, bacterial                | None   | Recovered |
| 11-156 7645            | 63 M     | 1            | Asthma                              | None   | Recovered |
| 11-157 6531            | 79 F     | 9            | Death                               | None   | Death     |
|                        |          | 4            | Edema, pulmonary                    |        |           |
|                        |          | 8            | Shock, cardiogenic                  |        |           |
|                        |          | 2            | Drug overdose                       |        |           |
| 11-158 4946            | 77 M     | 2            | Headache                            | D/C'd  | Recovered |
|                        |          | 2            | Vertigo                             |        |           |
|                        |          | 2            | Nystagmus                           |        |           |
| 11-160 5123            | 49 M     | 28           | Death                               | None   | Death     |
|                        |          | 28           | Myocardial infarction               |        |           |
| 11-160 5130            | 58 M     | 26           | Death                               | None   | Death     |
|                        |          | 26           | Cardiac arrest                      |        |           |
| 11-160 5562            | 67 F     | 12           | Myocardial infarction, non-Q-wave   | None   | Recovered |
| 11-161 5139            | 87 F     | 20           | Angina pectoris                     | None   | Recovered |
| 11-161 5140            | 83 F     | 6            | GI hemorrhage, anal/rectal          | None   | Recovered |
|                        |          | 16           | Pain, chest                         |        |           |
| 11-163 5192            | 70 M     | 8            | Death                               | None   | Death     |
|                        |          | 8            | Rupture, myocardial                 |        |           |
| 11-164 5537            | 71 F     | 5            | Angina, unstable                    | None   | Recovered |
| 11-168 6750            | 63 F     | 1            | Drug overdose                       | None   | Recovered |
| 11-168 6774            | 65 M     | 9            | Embolism                            | None   | Recovered |
| 11-168 6840            | 76 F     | 26           | Heart failure                       | None   | Recovered |
|                        |          | 26           | Effusion, pleural                   |        |           |
| 11-168 6990            | 55 M     | 13           | Angina pectoris                     | None   | Recovered |
|                        |          | 24           | Angina pectoris                     |        |           |
| 11-170 6819            | 75 M     | 4            | Death                               | None   | Death     |
|                        |          | 3            | Cardiac arrest                      |        |           |
|                        |          | 2            | Heart failure                       |        |           |
|                        |          | 3            | Shock, cardiogenic                  |        |           |
| 11-170 6873            | 58 M     | 11           | Respiratory failure                 | None   | Recovered |
| 11-171 6823            | 47 F     | 15           | Angina, unstable                    | None   | Recovered |
| 11-172 6846            | 84 F     | 13           | Death                               | None   | Death     |
|                        |          | 13           | Cardiac arrest                      |        |           |
| 11-172 6895            | 57 M     | 25           | Bigeminy/trigeminy/<br>quadrigeminy | None   | Recovered |
|                        |          | 25           | Heart failure                       |        |           |
|                        |          | 25           | Infection, wound                    |        |           |
|                        |          | 25           | Arthropathy, traumatic              |        |           |
| 11-175 7247            | 72 M     | 27           | Edema, pulmonary                    | None   | Recovered |
| 11-178 7514            | 69 F     | 19           | Pain, abdominal                     | None   | Recovered |
|                        |          | 2            | Drug overdose                       |        |           |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject # | Age/ Sex | Day of Onset             | Adverse Experience                                                                     | Action | Outcome    |
|------------------------|----------|--------------------------|----------------------------------------------------------------------------------------|--------|------------|
| <b>HEPARIN ALONE</b>   |          |                          |                                                                                        |        |            |
| <i>RESTORE Trial</i>   |          |                          |                                                                                        |        |            |
| 013-003 1012           | 71 M     | 2<br>3                   | Pneumonia, aspiration<br>Hemoptysis                                                    | None   | Recovered  |
| 013-003 1281           | 73 M     | 21                       | Angina pectoris                                                                        | None   | Recovered  |
| 013-003 2077           | 74 M     | 1                        | CVA, hemorrhagic                                                                       | D/C'd  | Recovered  |
| 013-003 2252           | 83 F     | 3                        | Weakness, muscle                                                                       | None   | Continuing |
| 013-006 1068           | 74 M     | 17                       | Dizziness<br>Pain, chest                                                               | None   | Recovered  |
| 013-007 1307           | 44 M     | 22                       | Occlusion, arterial                                                                    | None   | Recovered  |
| 013-008 1721           | 43 M     | 1<br>6<br>6<br>18        | Drug overdose<br>Pain, chest<br>Occlusion, coronary artery<br>Pain, chest              | None   | Recovered  |
| 013-009 1323           | 56 M     | 2<br>2                   | Cardiac arrest<br>Arrhythmia                                                           | None   | Recovered  |
| 013-009 1563           | 61 M     | 5                        | Angina pectoris                                                                        | None   | Recovered  |
| 013-009 1568           | 75 M     | 12                       | Bronchitis                                                                             | None   | Recovered  |
| 013-009 2136           | 35 M     | 2<br>2                   | Shock, cardiogenic<br>Asystole                                                         | D/C'd  | Recovered  |
| 013-009 2567           | 60 M     | 2                        | Dissection, coronary artery                                                            | None   | Recovered  |
| 013-009 2569           | 57 F     | 18                       | Pain, chest                                                                            | None   | Recovered  |
| 013-009 2578           | 42 M     | 6                        | Angina pectoris                                                                        | None   | Recovered  |
| 013-009 3224           | 65 F     | 12                       | Hematochezia                                                                           | None   | Recovered  |
| 013-011 1521           | 67 M     | 15                       | Claudication, intermittent                                                             | None   | Recovered  |
| 013-013 2228           | 46 M     | 28                       | Dyspnea                                                                                | None   | Recovered  |
| 013-013 2230           | 66 F     | 25                       | Pain, chest                                                                            | None   | Recovered  |
| 013-013 3184           | 71 M     | 23<br>27                 | Myocardial infarction<br>Vascular disorder                                             | None   | Recovered  |
| 013-014 1424           | 62 F     | 12                       | Discoloration, skin                                                                    | None   | Recovered  |
| 013-014 1425           | 68 F     | 4<br>9<br>12<br>13<br>18 | Septicemia<br>Hemorrhage<br>Thrombocytopenia<br>Hemorrhage, gastrointestinal<br>Death  | None   | Recovered  |
| 013-014 1842           | 59 M     |                          | Pain, chest                                                                            | None   | Continuing |
| 013-014 1846           | 39 M     | 28                       | Angina, unstable                                                                       | None   | Recovered  |
| 013-014 2163           | 70 M     | 29                       | Anxiety                                                                                | None   | Recovered  |
| 013-014 2379           | 76 M     | 15                       | Heart failure                                                                          | None   | Recovered  |
| 013-014 3256           | 59 M     | 14                       | Pericarditis                                                                           | None   | Recovered  |
| 013-014 3499           | 84 M     | 32                       | Pain, toe                                                                              | None   | Recovered  |
| 013-019 1115           | 49 F     | 9                        | Hyperventilation                                                                       | None   | Recovered  |
| 013-020 1371           | 58 M     | 25                       | Angina pectoris                                                                        | None   | Recovered  |
| 013-020 1374           | 67 F     | 1                        | Dissection, coronary artery                                                            | D/C'd  | Recovered  |
| 013-020 1375           | 55 M     | 30                       | Angina pectoris                                                                        | None   | Recovered  |
| 013-020 2530           | 41 F     | 4                        | Angina, unstable                                                                       | None   | Recovered  |
| 013-020 2932           | 58 M     | 2<br>2<br>2<br>2<br>2    | Death<br>Heart failure<br>AV conduction disorder<br>Rales/rhonchi<br>Cardiogenic shock | D/C'd  | Death      |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject # | Age/ Sex | Day of Onset          | Adverse Experience                                                          | Action | Outcome    |
|------------------------|----------|-----------------------|-----------------------------------------------------------------------------|--------|------------|
| <b>HEPARIN ALONE</b>   |          |                       |                                                                             |        |            |
| <b>RESTORE Trial</b>   |          |                       |                                                                             |        |            |
| 013-021 2700           | 56 F     | 3<br>25               | Infection, urinary tract<br>Neoplasm, intestinal, malignant                 | None   | Continuing |
| 013-021 3734           | 62 M     | 2<br>2                | Fever<br>Pericarditis                                                       | None   | Recovered  |
| 013-022 1248           | 66 M     | 2<br>27               | 6<br>Pain, chest<br>Vascular disorder                                       | None   | Continuing |
| 013-025 1850           | 78 M     | 1                     | Bleeding, postoperative                                                     | None   | Recovered  |
| 013-026 1992           | 45 M     | 1<br>3                | Dissection, coronary artery<br>Pain, chest                                  | D/C'd  | Recovered  |
| 013-026 3653           | 77 F     | 1<br>16               | Dissection, coronary artery<br>Asthenia/fatigue                             | D/C'd  | Recovered  |
| 013-027 1158           | 58 M     | 1                     | Cardiac tamponade                                                           | D/C'd  | Recovered  |
| 013-027 1158           | 58 M     | 1                     | Surgery, heart vessel, complication                                         | D/C'd  | Recovered  |
| 013-027 1615           | 47 M     | 8                     | Urolithiasis                                                                | None   | Recovered  |
| 013-027 1620           | 71 F     | 25                    | Vascular insufficiency, intestinal                                          | None   | Recovered  |
| 013-027 2030           | 61 M     | 26                    | Pain, chest                                                                 | None   | Recovered  |
| 013-027 3328           | 43 M     | 1<br>17<br>18         | Occlusion, coronary artery<br>Syncope<br>Urolithiasis                       | D/C'd  | Recovered  |
| 013-028 1643           | 63 F     | 10<br>19              | Pain, arm<br>Pain, chest                                                    | None   | Recovered  |
| 013-030 1107           | 61 F     | 21                    | Angina pectoris                                                             | None   | Recovered  |
| 013-030 1437           | 62 M     | 29                    | Pain, chest                                                                 | None   | Recovered  |
| 013-030 1441           | 71 M     | 1                     | Ventricular tachycardia                                                     | None   | Recovered  |
| 013-030 1445           | 71 F     | 1<br>2<br>2<br>2      | Hemorrhage, retroperitoneal<br>Death<br>Thrombocytopenia<br>Hemorrhage      | D/C'd  | Death      |
| 013-030 2094           | 61 F     | 1                     | Dissection, coronary artery                                                 | D/C'd  | Recovered  |
| 013-030 2314           | 68 F     | 3<br>3<br>3           | Cardiac arrest<br>Dyspnea<br>Renal insufficiency                            | None   | Continuing |
| 013-030 2680           | 61 M     | 23                    | Pain, chest                                                                 | None   | Recovered  |
| 013-030 2689           | 72 M     | 1<br>2                | Occlusion, coronary artery<br>Ventricular tachycardia                       | D/C'd  | Recovered  |
| 013-030 3341           | 55 M     | 1                     | Pain, chest                                                                 | None   | Recovered  |
| 013-030 3356           | 53 M     | 1                     | Ventricular tachycardia                                                     |        |            |
| 013-030 3356           | 53 M     | 2                     | ECG abnormality                                                             | None   | Recovered  |
| 013-031 1830           | 65 F     | 29                    | Pain, chest                                                                 | None   | Recovered  |
| 013-031 1830           | 65 F     | 29<br>29              | Dyspnea<br>Pain, neck                                                       | None   | Recovered  |
| 013-031 1997           | 53 M     | 13<br>13              | Asthenia/fatigue<br>Pain, chest                                             | None   | Recovered  |
| 013-031 2742           | 74 M     | 2<br>2<br>2<br>2<br>2 | BUN increased<br>Cardiac output<br>Heart failure<br>Pneumonia<br>Bronchitis | None   | Recovered  |
| 013-032 2097           | 54 M     | 14<br>14              | Pain, chest<br>Vascular disorder                                            | None   | Recovered  |
| 013-032 2099           | 48 M     | 1<br>1                | Dissection, coronary artery<br>Pain, chest                                  | D/C'd  | Recovered  |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject # | Age/ Sex | Day of Onset   | Adverse Experience                                          | Action | Outcome    |
|------------------------|----------|----------------|-------------------------------------------------------------|--------|------------|
| <b>HEPARIN ALONE</b>   |          |                |                                                             |        |            |
| <i>RESTORE Trial</i>   |          |                |                                                             |        |            |
| 013-032 2328           | 50 F     | 1              | Dissection, coronary artery                                 | D/C'd  | Recovered  |
| 013-036 1555           | 74 F     | 1<br>1         | Hematoma<br>Hypotension                                     | D/C'd  | Recovered  |
| 013-037 1783           | 75 M     | 1<br>1<br>6    | Bradycardia<br>Hypotension<br>Pain, chest                   | None   | Recovered  |
| 013-037 1785           | 71 F     | 4              | Pain, chest                                                 | None   | Recovered  |
| 013-039 1630           | 74 M     | 3              | Fever                                                       | None   | Recovered  |
| 013-039 2180           | 67 F     | 12<br>12       | Dyspnea<br>Pain, chest                                      | None   | Recovered  |
| 013-039 2275           | 74 F     | 30             | Pain, shoulder                                              | None   | Recovered  |
| 013-039 2671           | 45 M     | 2              | Drug overdose                                               | None   | Recovered  |
| 013-041 1212           | 51 M     | 31             | Trauma                                                      | None   | Continuing |
| 013-041 1218           | 49 M     | 1              | Pain, chest                                                 | None   | Recovered  |
| 013-041 2073           | 73 M     | 1              | Dissection, coronary artery                                 | D/C'd  | Recovered  |
| 013-042 1342           | 56 M     | 1              | Dissection, coronary artery                                 | D/C'd  | Recovered  |
| 013-045 1314           | 53 M     | 10<br>22<br>22 | Fever<br>Myocardial infarction<br>Death                     | None   | Death      |
| 013-045 3273           | 76 F     | 3              | Pain, abdominal                                             |        |            |
| 013-046 2406           | 49 M     | 1              | Dissection, coronary artery                                 | D/C'd  | Recovered  |
| 013-047 1298           | 71 M     | 1              | Angina pectoris                                             | None   | Recovered  |
| 013-047 2106           | 61 F     | 21             | Angina pectoris                                             |        |            |
| 013-048 2045           | 72 M     | 17<br>25       | Pain, chest<br>Angina pectoris                              | None   | Recovered  |
| 013-048 2051           | 70 M     | 13             | Pain, chest                                                 | None   | Recovered  |
| 013-049 1389           | 67 F     | 13             | Pain, chest                                                 | None   | Recovered  |
| 013-051 1053           | 67 F     | 1<br>2<br>17   | Dissection, coronary artery<br>Hematuria<br>Pain, chest     | D/C'd  | Recovered  |
| 013-051 1057           | 58 F     |                | Hematuria                                                   | None   | Recovered  |
| 013-051 1683           | 69 M     | 1              | Dissection, coronary artery                                 | D/C'd  | Recovered  |
| 013-051 1686           | 73 M     | 2              | Drug overdose                                               | None   | Recovered  |
| 013-051 1689           | 60 F     | 3              | Respiratory distress syndrome                               | None   | Recovered  |
| 013-051 1689           | 60 F     | 3              | Septicemia                                                  | None   | Recovered  |
| 013-052 1703           | 59 M     | 1              | Dissection, coronary artery                                 | D/C'd  | Recovered  |
| 013-052 1703           | 59 M     | 20             | Hemorrhage, gastrointestinal                                | None   | Recovered  |
| 013-052 2903           | 64 F     | 2<br>2<br>3    | Ventricular tachycardia<br>Bleeding, postoperative<br>Death | D/C'd  | Death      |
| 013-053 1463           | 60 F     | 13             | Angina, unstable                                            | None   | Recovered  |
| 013-053 1473           | 59 F     | 1              | Dissection, coronary artery                                 | None   | Recovered  |
| 013-053 1948           | 60 M     | 1              | Dissection, coronary artery                                 | None   | Recovered  |
| 013-053 1954           | 71 M     | 24<br>26       | CVA<br>Death                                                | D/C'd  | Death      |
| 013-053 2297           | 67 M     | 1<br>15        | Dissection, coronary artery<br>Pain, chest                  | None   | Recovered  |
| 013-053 2911           | 68 F     | 3              | Renal insufficiency                                         | None   | Recovered  |
| 013-055 2886           | 47 M     | 20             | Pain, chest                                                 | None   | Recovered  |
| 013-055 2889           | 56 M     | 14             | Pain, chest                                                 | None   | Recovered  |
| 013-0561173            | 67 F     | 1              | Min Dissection, coronary artery                             | D/C'd  | Recovered  |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/ Subject #  | Age/ Sex  | Day of Onset | Adverse Experience                | Action | Outcome    |
|----------------------|-----------|--------------|-----------------------------------|--------|------------|
| <b>HEPARIN ALONE</b> |           |              |                                   |        |            |
| <i>RESTORE Trial</i> |           |              |                                   |        |            |
| 013-056 1179         | 56 M      | 3            | Weakness, muscle                  | None   | Recovered  |
| 013-056 1451         | 50 M      | 1            | Dissection, coronary artery       | D/C'd  | Recovered  |
| 013-056 1458         | 79 M      | 3            | Pseudoaneurysm                    | None   | Recovered  |
| 013-056 1761         | 63 M      | 1            | Surgery Mod.                      | D/C'd  | Recovered  |
|                      |           | 1            | Embolism, popliteal               |        |            |
| 013-056 2197         | 74 M      | 12           | Pain, abdominal                   | None   | Recovered  |
| 013-058 2846         | 55 M      | 13           | Pain, chest                       | None   | Recovered  |
| 013-059 1073         | 64 M      | 2            | Dissection, coronary artery       | None   | Recovered  |
| 013-059 1078         | 46 M      | 10           | Pain, chest                       | None   | Recovered  |
|                      |           | 11           | Pain, chest                       |        |            |
| 013-059 1080         | 73 M      | 5            | Myocardial infarction             | None   | Recovered  |
|                      |           | 28           | Atrial fibrillation               |        |            |
| 013-059 1080         | 73 M      | 28           | Pain, chest                       | None   | Recovered  |
| 013-060 1161         | 28 F      | 10           | Pain, chest                       | None   | Recovered  |
| 013-060 2995         | 47 M      | 23           | Dissection, coronary artery       | None   | Recovered  |
| 013-060 2999         | 59 F      | 2            | Rash                              | None   | Recovered  |
|                      |           | 3            | Fever                             |        |            |
| 013-061 3058         | 39 M      | 9            | Pain, chest                       | None   | Recovered  |
| 013-061 3063         | 61 M      | 31           | Pain, chest                       | None   | Recovered  |
| 013-062 1414         | 71 F      | 2            | Hemorrhage                        | D/C'd  | Recovered  |
| 013-062 2424         | 67 M      | 1            | Dissection, coronary artery       | None   | Continuing |
| 013-062 2425         | 68 M      | 1            | Dissection, coronary artery       | None   | Continuing |
|                      |           | 8            | Pain, chest                       |        |            |
|                      |           | 8            | Heart failure                     |        |            |
|                      |           | 29           | Pain, chest                       |        |            |
| 013-062 2986         | 58 M      | 3            | Fistula, arteriovenous            | None   | Recovered  |
| 013-062 3934         | 68 F      | 1            | Dissection, coronary artery       | D/C'd  | Recovered  |
| None                 | Recovered | 3            | Barrett's esophagus               | None   | Recovered  |
| 013-064 1779         | 54 M      | 1            | Dissection, coronary artery       | D/C'd  | Recovered  |
| 013-067 2014         | 65 F      | 4            | Infection, urinary tract          | None   | Recovered  |
| 013-067 2430         | 67M       | 5            | Pain, chest                       | None   | Recovered  |
| 013-069 3369         | 48 M      | 1            | Hrs Dissection, coronary artery   | None   | Recovered  |
|                      |           | 2            | Premature ventricular contraction |        |            |
|                      |           | 19           | Dyspepsia                         |        |            |
| 013-070 2447         | 50 F      | 9            | Pain, leg                         | None   | Recovered  |
|                      |           | 9            | Edema/swelling                    |        |            |
|                      |           | 30           | Angina, unstable                  |        |            |
| 013-070 2454         | 65 F      | 24           | Pain, chest                       | None   | Recovered  |
| 013-070 2456         | 71 M      | 2            | Renal insufficiency, acute        | D/C'd  | Recovered  |
|                      |           | 2            | Respiratory distress              |        | Recovered  |
|                      |           | 3            | Urinary retention                 |        | Continuing |
| 013-071 3901         | 58 M      | 2            | Hemorrhage                        | D/C'd  | Recovered  |
|                      |           | 2            | Bleeding, postoperative           |        |            |
| 013-072 1898         | 70 F      | 2            | Hypotension                       | None   | Recovered  |
| 013-072 1899         | 46 M      | 1            | Dissection, coronary artery       | None   | Recovered  |
|                      |           | 3            | Hemorrhage                        |        |            |
| 013-073 1637         | 74 F      | 7            | Pain, chest                       | None   | Recovered  |
| 013-076 1514         | 62 M      | 21 2H        | Reflux esophagitis                | None   | Recovered  |
| 013-076 1515         | 63 F      | 21           | Asthenia/fatigue                  | None   | Recovered  |
|                      |           | 29           | Asthenia/fatigue                  |        |            |
| 013-077 1531         | 53 M      | 1            | Drug overdose                     | None   | Recovered  |
|                      |           | 7            | Hemorrhage, retroperitoneal       |        |            |

15.0.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject # | Age/ Sex | Day of Onset | Adverse Experience                                  | Action | Outcome    |
|------------------------|----------|--------------|-----------------------------------------------------|--------|------------|
| <b>HEPARIN ALONE</b>   |          |              |                                                     |        |            |
| <i>RESTORE Trial</i>   |          |              |                                                     |        |            |
| 013-077 1533           | 48 M     | 1            | Drug overdose                                       | None   | Recovered  |
| 013-077 1535           | 62 M     | 1            | Drug overdose                                       | None   | Recovered  |
| 013-077 1537           | 75 M     | 1<br>2       | Drug overdose<br>Hemorrhage                         | None   | Recovered  |
| 013-077 1540           | 63 M     | 1<br>13      | Min Drug overdose<br>Pain, chest                    | None   | Recovered  |
| 013-077 1691           | 66 M     | 1            | Drug overdose                                       | None   | Recovered  |
| 013-077 1693           | 69 M     | 1            | Drug overdose                                       | None   | Recovered  |
| 013-080 1506           | 45 F     | 11           | Pain, chest                                         | None   | Recovered  |
| 013-080 1506           | 45 F     | 11<br>11     | Myocardial infarction<br>Occlusion, coronary artery | None   | Recovered  |
| 013-082 1658           | 61 M     | 1<br>1       | Pseudoaneurysm<br>Bleeding, postoperative           | None   | Recovered  |
| 013-082 1659           | 79 F     | 7<br>7       | Days Angina pectoris<br>Atherosclerosis, coronary   | None   | Recovered  |
| 013-082 3751           | 75 F     | 1            | Ventricular fibrillation                            | None   | Recovered  |
| 013-082 3751           | 75 F     | 1            | Ventricular tachycardia                             | None   | Recovered  |
| 013-084 3034           | 39 M     | 1            | Dissection, coronary artery                         | D/C'd  | Recovered  |
| 013-085 1960           | 55 F     | 5            | Embolism/infarction, pulmonary                      | None   | Recovered  |
| 013-085 3856           | 39 M     | 2<br>2       | Pain, chest<br>Pain, chest                          | None   | Recovered  |
| 013-086 1836           | 73 M     | 2<br>2       | Hemorrhage<br>Bleeding, postoperative               | None   | Recovered  |
| 013-087 2220           | 52 M     | 3            | Atrial tachycardia                                  | None   | Recovered  |
| 013-087 2775           | 57 F     | 3            | Pain, chest                                         | None   | Recovered  |
| 013-087 2777           | 52 M     | 10<br>31     | Pain, chest<br>Pain, chest                          | None   | Recovered  |
| 013-088 2878           | 55 M     | 1<br>15      | Dissection, coronary artery<br>Infection, pelvic    | None   | Recovered  |
| 013-088 2881           | 64 M     | 1<br>1       | Anaphylaxis<br>CVA                                  | D/C'd  | Continuing |
| 013-089 2062           | 63 F     | 9            | Pyelonephritis                                      | None   | Recovered  |
| 013-089 2555           | 52 F     | 2            | Drug overdose                                       | None   | Recovered  |
| 013-089 2561           | 63 F     | 1            | Dissection, coronary artery                         | None   | Recovered  |
| 013-089 2564           | 60 M     | 24           | Angina pectoris                                     | None   | Recovered  |
| 013-089 3908           | 72 F     | 6<br>6       | Bleeding, postoperative<br>Pseudoaneurysm           | None   | Continuing |
| 013-091 1743           | 48 M     | 1            | Dissection, coronary artery                         | None   | Recovered  |
| 013-091 1750           | 66 M     | 2            | Hrs Myocardial infarction                           | None   | Recovered  |
| 013-093 2017           | 65 F     | 1            | Dissection, coronary artery                         | None   | Recovered  |
| 013-096 2460           | 55 F     | 15           | Angina pectoris                                     | None   | Recovered  |
| 013-098 2435           | 51 M     | 4            | Myocardial infarction                               | None   | Recovered  |
| 013-099 2588           | 50 M     | 19           | Pain, chest                                         | None   | Recovered  |
| 013-100 2054           | 76 M     | 2            | Angina pectoris                                     | None   | Recovered  |
| 013-100 2055           | 72 M     | 1            | Dissection, coronary artery                         | None   | Recovered  |
| 013-101 2107           | 48 M     | 1            | Occlusion, coronary artery                          | None   | Recovered  |
| 013-101 2213           | 73 F     | 30<br>30     | Pain, chest<br>Dyspnea                              | None   | Recovered  |
| 013-101 3128           | 49 M     | 19<br>22     | Pain, chest<br>Ventricular tachycardia              | None   | Recovered  |

150.3 Subjects in Heparin Group with Serious Adverse Events (SAEs)

Table 15.0.2.1 SAEs in the heparin group from the phase III trials (cont).

| Protocol/<br>Subject # | Age/ Sex | Day of Onset | Adverse Experience                                         | Action | Outcome                 |
|------------------------|----------|--------------|------------------------------------------------------------|--------|-------------------------|
| <b>HEPARIN ALONE</b>   |          |              |                                                            |        |                         |
| <i>RESTORE Trial</i>   |          |              |                                                            |        |                         |
| 013-106 5204           | 55 M     | 8            | Ventricular fibrillation                                   | None   | Recovered               |
| 013-107 5243           | 79 M     | 1<br>2<br>4  | Heart failure<br>Bradycardia<br>Death                      | None   | Death                   |
| 013-109 5098           | 63 M     | 1            | Drug overdose                                              | None   | Recovered               |
| 013-109 5109           | 67 F     | 13<br>13     | Death<br>Ventricular fibrillation                          | None   | Death                   |
| 013-110 5045           | 63 M     | 1<br>2       | Dissection, coronary artery<br>Hemorrhage, retroperitoneal | None   | Continuing<br>Recovered |
| 013-115 5643           | 70 M     | 3<br>3       | Cholecystitis<br>Cholecystitis                             | None   | Recovered               |
| 013-115 5649           | 49 M 3   | 3            | Fistula, arteriovenous                                     | None   | Continuing              |
| 013-116 5679           | 78 F     | 26           | Aneurysm                                                   | None   | Recovered               |
| 013-120 3306           | 52 M     | 16           | Angina, unstable                                           | None   | Recovered               |
| 013-120 3663           | 59 M     | 1            | Occlusion, coronary artery                                 | D/C'd  | Recovered               |
| 013-120 3775           | 77 F     | 3            | Hemorrhage, subdural                                       | None   | Recovered               |

15.1 AEs associated with lab abnormalities

| Protocol/<br>Subject #          | Age/ Sex | Day of Onset          | Adverse Experience                                                                                                     | Action |
|---------------------------------|----------|-----------------------|------------------------------------------------------------------------------------------------------------------------|--------|
| <b>PRISM-PLUS Trial</b>         |          |                       |                                                                                                                        |        |
| <b>Heparin group</b>            |          |                       |                                                                                                                        |        |
| AN 5072                         | 88/F     | 4                     | Fecal occult blood                                                                                                     | None   |
| AN 5196                         | 66/F     | 4                     | Hemoglobin decreased                                                                                                   | None   |
| AN 1569                         | 79/M     | 4                     | Hematocrit decreased                                                                                                   | None   |
| <b>PRISM Trial</b>              |          |                       |                                                                                                                        |        |
| <b>Tirofiban group</b>          |          |                       |                                                                                                                        |        |
| AN 1014                         | 71/F     | 3<br>4<br>5           | Leukocyte count increased<br>Leukocyte count increased<br>Leukocyte count increased                                    | None   |
| AN 1462                         | 51/F     | 1                     | Platelet count decreased                                                                                               | D/C'd  |
| AN 2436                         | 85/F     | 5                     | Fecal occult blood                                                                                                     | None   |
| AN 3252                         | 56/M     | 17                    | Prothrombin time increased                                                                                             | None   |
| AN 4402                         | 64/F     | 10<br>10              | Hemoglobin decreased<br>Hemoglobind decreased                                                                          | None   |
| AN 2319                         | 43/F     | 5                     | Hyperkalemia                                                                                                           | None   |
| AN 5297                         | 79/M     | 1<br>2                | Platelet count decreased<br>Platelet count decreased                                                                   | None   |
| AN 4543                         | 56/M     | 4                     | Hematuria                                                                                                              | None   |
| <b>Heparin group</b>            |          |                       |                                                                                                                        |        |
| AN1047                          | 72/M     | 5<br>5                | Hemoglobin decreased<br>Hematocrit decreased                                                                           | None   |
| AN 1169                         | 65/M     | 9                     | Prothrombin time increased                                                                                             | None   |
| AN 7627                         | 66/M     | 18                    | Fecal occult blood                                                                                                     | None   |
| AN 2260                         | 55/F     | 1                     | Hyperkalemia                                                                                                           | None   |
| <b>RESTORE Trial</b>            |          |                       |                                                                                                                        |        |
| <b>Tirofiban +Heparin group</b> |          |                       |                                                                                                                        |        |
| AN 1564                         | 50/M     | 1                     | Thrombocytopenia                                                                                                       | D/C'd  |
| AN 1924                         | 67/M     | 1<br>2                | Thrombocytopenia<br>Thrombocytopenia                                                                                   | D/C'd  |
| AN 3996                         | 75/F     | 1                     | Thrombocytopenia                                                                                                       | D/C'd  |
| AN 5265                         | 67/M     | 1                     | aPTT increased                                                                                                         | None   |
| <b>Placebo +Heparin group</b>   |          |                       |                                                                                                                        |        |
| AN 1012                         | 71/M     | 3                     | Hyperphosphatemia                                                                                                      | None   |
| AN 1057                         | 58/F     | 3                     | Hematuria                                                                                                              | None   |
| AN 2104                         | 56/M     | 3                     | Creatine phosphokinase increased                                                                                       | None   |
| AN 5643                         | 70/M     | 3<br>5<br>5<br>4<br>4 | Leukocyte count increased<br>Leukocyte count increased<br>Lymphocyte count increased<br>AST increased<br>ALT increased | None   |

## 16.0 Appendix Four: Discontinuations for Clinical AEs.

The table below summarizes the subjects with clinical Adverse Events leading to discontinuation of study drug, and is based on data provided by the sponsor. It has not been independently verified by the FDA.

The following sources were used for this appendix:

1. NDA volume 1.42, table 47 (PRISM-PLUS);
2. NDA volume 1.48, table 46 (PRISM);
3. NDA volume 1.55 table 42 (RESTORE).

Note that the number of subjects discontinued due to adverse events in the RESTORE trial was much higher than the number in either the PRISM or PRISM-PLUS trials.

### 16.0.1 Subjects In Tirofiban Group Discontinued After Clinical AEs

Table 16.0.1.1 Discontinuations for clinical AEs in the tirofiban group from phase III studies.

| Protocol/<br>Subject #  | Age/Sex | Day of Onset | Adverse Experience             | Outcome    |
|-------------------------|---------|--------------|--------------------------------|------------|
| <b>TIROFIBAN GROUP</b>  |         |              |                                |            |
| <b>PRISM-PLUS TRIAL</b> |         |              |                                |            |
| 006-032 6368            | 70 F    | 3            | Hemorrhage, gastric            | Recovered  |
|                         | 77 F    | 4            | Cerebrovascular accident       | Recovered  |
| 006-032 6623            |         |              |                                |            |
| 006-034 6630            | 85 F    | 2            | ematuria                       | Recovered  |
| 006-037 6079            | 82 F    | 2            | Epistaxis                      | Recovered  |
| 006-044 6250            | 73 M    | 4            | Hemorrhage, anal/rectal        | Recovered  |
| 006-044 7083            | 79 M    | 4            | Bleeding, postoperative        | Continuing |
| 006-047 5180            | 72 M    | 2            | Thrombocytopenia               | Recovered  |
| 006-048 7246            | 69 M    | 2            | Edema, palate                  | Recovered  |
| 006-064 6584            | 74 M    | 2            | Embolism/infarction, pulmonary | Recovered  |
| <b>PRISM TRIAL</b>      |         |              |                                |            |
| 011-004 1117            | 71 M    | 2            | Hemorrhage, gastrointestinal   | Recovered  |
| 011-007 1458            | 52 M    | 1            | Thrombocytopenia               | Recovered  |
| 011-021 2131            | 65 M    | 3            | Hemorrhage, intracranial       | Recovered  |
| 011-058 1660            | 64 F    | 1            | Hemoptysis                     | Recovered  |
| 011-058 2421            | 55 M    | 2            | Hematuria                      | Recovered  |
| 011-061 3094            | 71 M    | 1            | Melena                         | Recovered  |
| 011-061 3623            | 81 M    | 1            | Hemorrhage, anal/rectal        | Recovered  |
| 011-062 3074            | 56 M    | 2            | Epistaxis                      | Recovered  |
| 011-065 4919            | 43 M    | 2            | Thrombocytopenia               | Recovered  |
| 011-065 4940            | 75 M    | 2            | Cardiac arrest                 | Recovered  |
| 011-069 4292            | 66 M    | 3            | Headache                       | Recovered  |
| 011-069 6655            | 79 F    | 1            | Drug overdose                  | Recovered  |
| 011-070 4369            | 42 M    | 2            | Pericarditis                   | Recovered  |
| 011-085 3360            | 45 M    | 2            | Thrombocytopenia               | Recovered  |
| 011-085 3477            | 65 M    | 1            | Thrombocytopenia               | Recovered  |
| 011-098 3034            | 66 M    | 2            | Hemorrhage, anal/rectal        | Recovered  |
| 011-109 1273            | 79 M    | 1            | Drug overdose                  | Recovered  |
| 011-120 5297            | 79 M    | 1            | Hematuria                      | Recovered  |
| 011-122 3425            | 72 M    | 1            | Embolism/infarction, pulmonary | Recovered  |
| 011-123 4462            | 83 F    | 2            | Dysfunctional uterine bleeding | Recovered  |
| 011-127 4553            | 46 F    | 2            | Drug overdose                  | Recovered  |
| 011-127 4557            | 64 M    | 2            | Epistaxis                      | Recovered  |
| 011-132 1341            | 69 F    | 2            | Epistaxis                      | Recovered  |

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### 16.0.1 Subjects In Tirofiban Group Discontinued After Clinical AEs

Table 16.0.1.1 Discontinuations for clinical AEs in tirofiban group from the phase III studies (cont).

| Protocol/<br>Subject #  | Age/ Sex | Day of Onset | Adverse Experience                  | Outcome   |
|-------------------------|----------|--------------|-------------------------------------|-----------|
| <b>TIROFIBAN GROUP</b>  |          |              |                                     |           |
| <b>PRISM-PLUS TRIAL</b> |          |              |                                     |           |
| 011-132 7778            | 72 F     | 1            | Fecal occult blood                  | Recovered |
| 011-142 1985            | 83 M     | 1            | Thrombocytopenia                    | Recovered |
| 011-146 3774            | 71 M     | 1            | Hemorrhage, gastrointestinal        | Recovered |
| 011-155 6792            | 57 M     | 1            | Allergy                             | Recovered |
| 011-156 2262            | 84 F     | 2            | Hemorrhage, gastrointestinal, lower | Recovered |
| 011-156 2346            | 66 F     | 3            | Petechiae                           | Recovered |
| 011-158 4947            | 55 M     | 2            | AV block, third degree              | Recovered |
| 011-163 5193            | 64 M     | 1            | Blood pressure decreased            | Recovered |
| 011-167 2543            | 67       | 1            | Nausea                              | Recovered |
| 011-167 7859            | 41 F     | 2            | Nausea                              | Recovered |
| 011-168 6928            | 58 M     | 2            | Pain                                | Recovered |
| 011-171 6757            | 54 M     | 3            | Hemorrhage, gingival                | Recovered |
| 011-172 6772            | 49 M     | 1            | Melena                              | Recovered |

### 16.0.2 Subjects In Tirofiban + Heparin Group Discontinued After Clinical AEs

Table 16.0.1.1 Discontinuations for clinical AEs in tirofiban +heparin group from the phase III studies.

| Protocol/<br>Subject #               | Age/<br>Sex | Day of<br>Onset | Adverse Experience                     | Outcome    |
|--------------------------------------|-------------|-----------------|----------------------------------------|------------|
| <b>TIROFIBAN +<br/>HEPARIN GROUP</b> |             |                 |                                        |            |
| <b>PRISM-PLUS</b>                    |             |                 |                                        |            |
| 006-004 5068                         | 72 M        | 1               | Thrombocytopenia                       | Recovered  |
| 006-004 5323                         | 72 F        | 2               | Hemoptysis                             | Recovered  |
| 006-004 5509                         | 75 M        | 2               | Confusion                              | Recovered  |
| 006-008 5374                         | 56 F        | 4               | Dissection, coronary artery            | Recovered  |
| 006-008 5376                         | 53 F        | 3               | Dissection, coronary artery            | Recovered  |
| 006-029 6473                         | 74 M        | 2               | Hematemesis                            | Recovered  |
| 006-029 6489                         | 68 F        | 2               | CVA                                    | Recovered  |
| 006-034 1630                         | 79 M        | 2               | Hematuria                              | Recovered  |
| 006-034 1631                         | 60 M        | 5               | Dissection, coronary artery            | Recovered  |
| 006-034 6980                         | 78 F        | 3               | Hemorrhage, vaginal                    | Recovered  |
| 006-035 6398                         | 79 M        | 2               | Hematuria                              | Recovered  |
| 006-041 6721                         | 77 M        | 1               | Ecchymosis                             | Continuing |
| 006-042 6509                         | 75 M        | 4               | Hematoma                               | Continuing |
| 006-043 6924                         | 88 F        | 1               | Blood dyscrasia                        | Recovered  |
| 006-044 1126                         | 64 M        | 3               | Hemorrhage, I.V. site                  | Continuing |
| 006-044 6242                         | 67 M        | 1               | Pyelonephritis, acute                  | Recovered  |
| 006-044 6278                         | 76 F        | 3               | Hemorrhage, gastrointestinal           | Recovered  |
| 006-044 6826                         | 60 F        | 4               | Dissection, coronary artery            | Recovered  |
| 006-045 1657                         | 52 M        | 5               | Surgery, heart vessel,<br>complication | Recovered  |
| 006-045 6289                         | 80 F        | 2               | Hematoma                               | Continuing |
| 006-047 5520                         | 72 F        | 4               | Hemorrhage, gastrointestinal           | Recovered  |
| 006-050 1622                         | 78 F        | 5               | Bleeding, postoperative                | Recovered  |
| 006-050 1623                         | 61 F        | 5               | Surgery, heart vessel,<br>complication | Recovered  |
| 006-050 1625                         | 54 M        | 5               | Dissection, coronary artery            | Recovered  |
| 006-055 6849                         | 61 F        |                 | Bleeding, postoperative                | Recovered  |

6.0.2 Subjects In Tirofiban + Heparin Group Discontinued After Clinical AEs

Table 16.0.1.1 Discontinuations for clinical AEs in tirofiban +heparin group from phase III studies (cont).

| Protocol/<br>Subject #               | Age/<br>Sex | Day of<br>Onset | Adverse Experience                         | Outcome    |
|--------------------------------------|-------------|-----------------|--------------------------------------------|------------|
| <b>TIROFIBAN +<br/>HEPARIN GROUP</b> |             |                 |                                            |            |
| <b>PRISM-PLUS</b>                    |             |                 |                                            |            |
| 006-057 1039                         | 48 M        | 5               | Bleeding, postoperative                    | Recovered  |
| 006-058 7395                         | 62 M        | 2               | Thrombocytopenia                           | Recovered  |
| 006-059 6329                         | 43 M        | 2               | Bleeding, Anal/rectal                      | Recovered  |
| 006-062 6530                         | 66 F        | 2               | Melena                                     | Recovered  |
| 006-062 6998                         | 53 M        | 4               | Bleeding, postoperative                    | Recovered  |
| 006-064 6953                         | 64 M        | 1               | Thrombocytopenia                           | Recovered  |
| 006-067 5288                         | 75 M        | 3               | Hematoma                                   | Recovered  |
| 006-078 1158                         | 47 F        |                 | Dysfunctional uterine<br>bleeding          | Recovered  |
| 006-084 7652                         | 77 M        | 2               | CVA                                        | Recovered  |
| 006-084 7797                         | 50 F        | 2               | Thrombocytopenia                           | Recovered  |
| 006-086 7553                         | 78 M        |                 | Cardiac arrest                             | Recovered  |
| 006-086 7818                         | 56 M        | 1               | Thrombocytopenia                           | Recovered  |
| 006-088 7594                         | 64 M        | 3               | Hemorrhage, gastrointestinal               | Recovered  |
| 006-089 7624                         | 72 F        | 2               | Bleeding, postoperative                    | Continuing |
| 006-092 7483                         | 77 M        | 5               | Ventricular fibrillation                   | Recovered  |
| 006-093 7445                         | 53 M        | 4               | Hematuria                                  | Recovered  |
| 006-093 7453                         | 65 M        | 3               | Hematuria                                  | Recovered  |
| <b>RESTORE TRIAL</b>                 |             |                 |                                            |            |
| 013-003 1286                         | 67M         | 2               | CVA, hemorrhagic                           | Continuing |
| 013-003 2947                         | 79M         | 2               | Chills<br>Fever<br>Tremor<br>Discoloration | Recovered  |
| 013-004 3749                         | 52F         | 1               | Dissection, coronary artery                | Recovered  |
| 013-007 1309                         | 61M         | 2               | Bleeding, postoperative                    | Recovered  |
| 013-008 1725                         | 67M         | 1               | Dissection, coronary artery                | Recovered  |
| 013-008 1730                         | 68 F        | 2               | Hemorrhage, gastrointestinal               | Continuing |
| 013-009 1569                         | 71 M        | 2               | Hematemesis                                | Recovered  |
| 013-011 1525                         | 53M         | 1               | Dissection, coronary artery                | Recovered  |
| 013-011 1528                         | 40M         | 1               | Dissection, coronary artery                | Recovered  |
| 013-011 1529                         | 56 M..      | 1               | Hematoma                                   | Recovered  |
| 013-013 3183                         | 41 F        | 1               | Ecchymosis<br>Bleeding, postoperative      | Recovered  |
| 013-014 1844                         | 69 M        | 1               | Hemorrhage, gastrointestinal               | Recovered  |
| 013-014 1848                         | 57 M        | 1               | Cardiac tamponade                          | Recovered  |
| 013-014 3760                         | 73 F        | 1               | Hematuria                                  | Recovered  |
| 013-014 2771                         | 50 F        | 2               | Bleeding, postoperative<br>Hematemesis     | Recovered  |
| 013-014 3255                         | 54 M        | 2               | Hematoma                                   | Recovered  |
| 013-014 3760                         | 71 M        | 1               | Hematoma<br>Bleeding, postoperative        | Recovered  |
| 013-014 3767                         | 66 F        | 1               | Hematemesis                                | Recovered  |
| 013-014 3996                         | 75 F        | 1               | Hemorrhage                                 | Continuing |

16.0.2 Subjects In Tirofiban + Heparin Group Discontinued After Clinical AEs

Table 16.0.1.1 Discontinuations for clinical AEs in tirofiban +heparin group from phase III studies (cont).

| Protocol/<br>Subject #               | Age/<br>Sex | Day of<br>Onset | Adverse Experience                                                         | Outcome    |
|--------------------------------------|-------------|-----------------|----------------------------------------------------------------------------|------------|
| <b>TIROFIBAN +<br/>HEPARIN GROUP</b> |             |                 |                                                                            |            |
| <b>RESTORE Trial</b>                 |             |                 |                                                                            |            |
| 013-015 1895                         | 66F         | 1               | Bleeding, postoperative                                                    | Recovered  |
| 013-018 1861                         | 70M         | 1               | Hematuria<br>Hemorrhage, oral<br>Bleeding, postoperative                   | Recovered  |
| 013-020 1594                         | 61 M        | 1               | Dissection, coronary artery                                                | Recovered  |
| 013-020 2927                         | 57 M        | 1               | Bleeding, postoperative                                                    | Recovered  |
| 013-020 2941                         | 65 M        | 1               | Bleeding, postoperative                                                    | Recovered  |
| 013-020 3148                         | 71 M        | 2               | Rash                                                                       | Recovered  |
| 013-021 1801                         | 74 F        | 1               | Dissection, coronary artery                                                | Recovered  |
| 013-021 1809                         | 73 M        | 1               | Hypotension                                                                | Recovered  |
| 013-021 2708                         | 77 F        | 1               | Bleeding, pharyngeal                                                       | Recovered  |
| 013-022 1247                         | 58 M        | 1               | Agitation                                                                  | Recovered  |
| 013-022 3102                         | 62 M        | 1               | Dissection, coronary artery<br>Effusion, pericardial<br>Shock, cardiogenic | Recovered  |
| 013-025 1942                         | 62 M        | 1               | Dissection, coronary artery                                                | Recovered  |
| 013-027 2504                         | 73 M        | 1               | Bleeding, postoperative<br>Hematemesis<br>Epistaxis<br>Hematuria           | Recovered  |
| 013-027 3302                         | 49M         | 1               | Blood pressure decreased                                                   | Recovered  |
| 013-030 1106                         | 83M         | 1               | Bleeding, postoperative                                                    | Continuing |
| 013-030 2690                         | 62F         | 2               | Hot flashes<br>Dermatitis                                                  | Recovered  |
| 013-031 1255                         | 37 M        | 1               | Chills                                                                     | Recovered  |
| 013-031 2256                         | 51M         | 1               | Epistaxis                                                                  | Recovered  |
| 013-031 3404                         | 49M         | 1               | Dissection, coronary artery                                                | Recovered  |
| 013-032 1757                         | 63M         | 2               | Confusion                                                                  | Recovered  |
| 013-039 1337                         | 58M         | 1               | Dissection, coronary artery                                                | Recovered  |
| 013-039 1624                         | 63M         | 1               | Bleeding, postoperative                                                    | Recovered  |
| 013-041 1211                         | 58F         | 2<br>2          | Hypotension<br>Bleeding, postoperative                                     | Recovered  |
| 013-041 1217                         | 51 F        | 1               | Hemorrhage                                                                 | Recovered  |
| 013-041 1219                         | 69M         | 1<br>1          | Dissection, coronary artery                                                | Recovered  |
| 013-041 2074                         | 56M         | 1<br>1          | Pharyngitis<br>Hemorrhage, oral                                            | Recovered  |
| 013-045 1313                         | 48F         | 1               | Dissection, coronary artery                                                | Recovered  |
| 013-046 2009                         | 77F         | 1               | Psychic disturbance                                                        | Recovered  |
|                                      | 48M         | 1               | Hypotension                                                                | Recovered  |
|                                      | 77F         | 1               | Hematoma                                                                   | Recovered  |
| 013-049 1382                         | 55 F        | 2               | Pseudoaneurysm                                                             | Recovered  |
|                                      | 49 M        | 2               | Bleeding, postoperative                                                    | Recovered  |
|                                      | 40 M        | 1               | Dissection, coronar                                                        |            |

16.02 Subjects In Tirofiban + Heparin Group Discontinued After Clinical AEs

Table 16.0.1.1 Discontinuations for clinical AEs in tirofiban +heparin group from phase III studies (cont).

| Protocol/<br>Subject #               | Age/<br>Sex | Day of<br>Onset | Adverse Experience                                         | Outcome    |
|--------------------------------------|-------------|-----------------|------------------------------------------------------------|------------|
| <b>TIROFIBAN +<br/>HEPARIN GROUP</b> |             |                 |                                                            |            |
| <b>RESTORE Trial</b>                 |             |                 |                                                            |            |
| 013-052 2905                         | 54M         | 1               | Dissection, coronary artery                                | Recovered  |
| 013-053 1951                         | 79M         | 1               | Surgery, heart vessel,<br>complication                     | Recovered  |
| 013-053 2907                         | 33 M        | 1               | Dissection, coronary artery                                | Recovered  |
| 013-053 2910                         | 51 M        | 1               | Dissection, coronary artery                                | Recovered  |
| 013-055 1036                         | 58 F        | 1               | Dissection, coronary artery                                | Recovered  |
| 013-055 2888                         | 55 M        |                 | Dissection, coronary artery                                | Recovered  |
| 013-058 1183                         | 53 M        | 1               | Dissection, coronary artery                                | Recovered  |
| 013-060 1162                         | 53 M        | 2<br>2          | Bleeding, postoperative<br>Bleeding, postoperative         | Recovered  |
| 013-060 2997                         | 64 M        | 1               | Bleeding, postoperative                                    | Recovered  |
| 013-061 1407                         | 61 F        | 2               | Hemorrhage, gingival                                       | Recovered  |
| 013-062 2661                         | 55 F        | 1               | Rupture, artery                                            | Recovered  |
| 013-064 1775                         | 47 F        | 1               | Hematoma                                                   | Continuing |
| 013-064 1777                         | 72 M        | 2<br>2<br>2     | Hemorrhage, retroperitoneal<br>Pain, abdominal<br>Hematoma | Continuing |
| 013-064 2492                         | 37 F        | 1               | Dissection, coronary artery                                | Recovered  |
| 013-066 2851                         | 71 M        | 2               | Hemorrhage, gastrointestinal                               | Recovered  |
| 013-066 3874                         | 74 F        | 1               | Dissection, coronary artery                                | Recovered  |
| 013-067 2643                         | 68 M        | 1               | Bleeding, postoperative                                    | Recovered  |
| 013-069 2537                         | 71 F        | 1               | Dissection, coronary artery                                | Recovered  |
| 013-070 2452                         | 49 M        | 1               | Dissection, coronary artery                                | Recovered  |
| 013-071 2594                         | 67 M        | 1               | Hematoma                                                   | Recovered  |
| 013-073 1638                         | 51 F        | 1               | Dissection, coronary artery                                | Recovered  |
| 013-073 3806                         | 75 F        | 1               | Pain, abdominal                                            | Recovered  |
| 013-080 1504                         | 65 F        | 1               | Dissection, coronary artery†                               | Recovered  |
| 013-080 1505                         | 56 M        | 1               | Dissection, coronary artery                                | Recovered  |
| 013-080 1925                         | 61 M        | 1               | Dissection, coronary artery                                | Recovered  |
| 013-087 2786                         | 42 M        | 1<br>1          | Occlusion, coronary artery<br>Dissection, coronary artery  | Continuing |
| 013-088 3731                         | 40 M        | 1               | Dissection, coronary artery                                | Recovered  |
| 013-090 2416                         | 59 F        | 1<br>1          | Hemorrhage<br>Bleeding, postoperative                      | Recovered  |
| 013-091 2860                         | 64 M        | 2<br>1          | Hemorrhage, gingival<br>Hematuria                          | Recovered  |
| 013-091 2861                         | 58F         | 1               | Dissection, coronary artery                                | Recovered  |
| 013-093 2018                         | 79 M        | 2               | Hematuria                                                  | Recovered  |
| 013-095 1545                         | 65 M        | 1               | Dissection, coronary artery                                | Recovered  |
| 013-098 2437                         | 75 M        | 2               | Melena                                                     | Recovered  |
| 013-100 2805                         | 66F         | 1               | Dissection, coronary artery                                | Recovered  |
| 013-101 2212                         | 68 M        | 1               | Dissection, coronary artery                                | Recovered  |
| 013-101 2214                         | 67 M        | 1               | Dissection, coronary artery                                | Recovered  |
| 013-103 5607                         | 67 F        | 1               | Pancreatitis                                               | Recovered  |
| 013-104 5007                         | 40 M        | 1               | Pericarditis                                               | Recovered  |

16.0.2 Subjects In **Tirofiban + Heparin** Group Discontinued After Clinical **AEs**

Table 16.0.1.1 Discontinuations for clinical AEs in tirofiban +heparin group from phase III studies (cont).

| Protocol/<br>Subject #               | Age/<br>Sex | Day of<br>Onset | Adverse Experience                  | Outcome    |
|--------------------------------------|-------------|-----------------|-------------------------------------|------------|
| <b>TIROFIBAN +<br/>HEPARIN GROUP</b> |             |                 |                                     |            |
| <i>RESTORE Trial</i>                 |             |                 |                                     |            |
| 013-105 5820                         | 43 M        | 2               | Infection, urinary tract            | Recovered  |
| 013-106 5202                         | 51 M        | 1               | Dissection, coronary artery         | Recovered  |
| 013-107 5251                         | 57 F        | 1               | Hematoma<br>Bleeding, postoperative | Recovered  |
| 013-109 5084                         | 58 F        | 1               | Dissection, coronary artery         | Recovered  |
| 013-110 5051                         | 57 M        | 1               | Hemopericardium                     | Recovered  |
| 013-113 2721                         | 77 M        | 1               | Dissection, coronary artery         | Recovered  |
| 013-114 5265                         | 67 F        | 1               | Hematoma                            | Recovered  |
| 013-116 5661                         | 65 M        | 2               | Bleeding, postoperative             | Continuing |
| 013-116 5669                         | 57 M        | 1               | — Dissection, coronary artery       | Recovered  |
| 013-116 5680                         | 54 M        | 1               | Dissection, coronary artery         | Recovered  |
| 013-116 5743                         | 46 M        | 1               | Dissection, coronary artery         | Recovered  |
| 013-118 3429                         | 45 M        | 2               | Hematoma                            | Continuing |
| 013-119 3644                         | 58 M        | 1               | Dissection, coronary artery         | Recovered  |
| 013-119 3812                         | 70 F        | 1               | Dissection, coronary artery         | Recovered  |

16.0.3 Subjects In Heparin Group Discontinued After Clinical **AEs**

Table 16.0.1.1 Discontinuations for clinical AEs in heparin group from phase III studies.

| Protocol/<br>Subject #  | Age/<br>Sex | Day of<br>Onset | Adverse Experience                      | Outcome    |
|-------------------------|-------------|-----------------|-----------------------------------------|------------|
| <b>HEPARIN GROUP</b>    |             |                 |                                         |            |
| <i>PRISM-PLUS TRIAL</i> |             |                 |                                         |            |
| 006-008 5474            | 78M         | 2               | Hematemesis                             | Recovered  |
| 006-011 5385            | 46M         | 2               | Impulse control disorder                | Recovered  |
| 006-034 6960            | 59M         | 3               | Effusion, pericardial                   | Continuing |
| 006-041 6709            | 72M         | 2               | Hematemesis                             | Recovered  |
| 006-041 6718            | 89 M        | 1               | Hematuria                               | Recovered  |
| 006-042 6354            | 75F         | 4               | Edema, pulmonary<br>Hypertensive crisis | Recovered  |
| 006-042 7047            | 78F         | 2               | Confusion                               | Recovered  |
| 006-045 7039            | 53M         | 3               | Burgery, heart vessel,<br>complication  | Recovered  |
| 006-046 7066            | 49M         | 4               | Cardiovascular hemodynamics<br>abn.     | Recovered  |
| 006-049 6506            | 80F         | 3               | Drug overdose                           | Recovered  |
| 006-053 5432            | 49F         | 1               | Pericarditis                            | Recovered  |
| 006-057 7026            | 69F         | 4               | Hematoma                                | Continuing |
| 006-058 6429            | 62 M        | 1               | Thrombocytopenia                        | Recovered  |
| 006-064 6583            | 79 F        | 3               | Hematoma                                | Recovered  |
| 006-065 6570            | 44 F        | 2               | Menstruation disorder                   | Continuing |
| 006-078 1708            | 79M         | 2               | Hematuria                               | Recovered  |
| 006-084 1234            | 69M         | 3               | Aneurysm, aortic                        | Recovered  |
| 006-084 753 1           | 68M         | 3               | CVA                                     | Recovered  |
| 006-084 7804            | 75M         | 1               | Heart failure                           | Recovered  |
| 006-093 7439            | 89F         | 2               | Edema, cerebral                         | Recovered  |

16.0.3 Subjects In Heparin Group Discontinued After Clinical AEs

Table 16.0.1.1 Discontinuations for clinical AEs in heparin group from phase III studies (cont).

| Protocol/<br>Subject # | Age/<br>Sex | Day of<br>Onset | Adverse Experience                                          | Outcome   |
|------------------------|-------------|-----------------|-------------------------------------------------------------|-----------|
| <b>HEPARIN GROUP</b>   |             |                 |                                                             |           |
| <i>PRISM TRIAL</i>     |             |                 |                                                             |           |
| 011-013 1277           | 65 M        | 2               | Confusion                                                   | Recovered |
| 011-021 2491           | 78 M        | 1               | Pain, chest                                                 | Recovered |
| 011-032 2433           | 48F         | 1               | Hematuria                                                   | Recovered |
| 011-061 3618           | 62M         | 2               | Hematuria                                                   | Recovered |
| 011-062 5109           | 63M         | 2               | Ulcer, gastric w/ hemorrhage                                | Recovered |
| 01 I-062 5395          | 56M         | 3               | Cholecystitis                                               | Recovered |
| 011-069 4294           | 72 F        | 1               | Embolism/infarction,<br>pulmonary                           | Recovered |
| 01 I-072 4363          | 77 M        | 2               | Confusion                                                   | Recovered |
| 011-092 1992           | 67 M        | 2               | Vomitin                                                     | Recovered |
| 01 I-115 4105          | 56 M        | 2               | Drug overdose                                               | Recovered |
| 011-118 2964           | 57 M        | 2               | Hemorrhage, I.V. site                                       | Recovered |
| 011-120 5715           | 64M         | 2               | Hematuria                                                   | Recovered |
| 011-125 5694           | 78M         | 3               | Edema, pulmonary                                            | Recovered |
| 011-127 4544           | 70 M        | 2               | Ventricular fibrillation                                    | Recovered |
| 01 I-127 5360          | 75 M        | 4               | Aneurysm, aortic                                            | Recovered |
| 011-156 2260           | 55 F 1      | 1               | Hypotension                                                 | Recovered |
| 011-158 4946           | 77 M        | 2               | Vertigo/Nystagmus                                           | Recovered |
| 011-161 5139           | 87 F        | 2               | Epistaxis                                                   | Recovered |
| 01 I-168 6983          | 75 F        | 2               | Confusion                                                   | Recovered |
| <i>RESTORE TRIAL</i>   |             |                 |                                                             |           |
| 013-003 2177           | 74M         | 1               | CVA, hemorrhagic                                            | Recovered |
| 013-009 2136           | 35M         | 2               | Asystole                                                    | Recovered |
| 013-014 1427           | 72 F        | 1               | Dissection, coronary artery                                 | Recovered |
| 013-017 2627           | 49 M        | 1               | Min Dissection, coronary<br>artery                          | Recovered |
| 013-020 1085           | 37 M        | 1               | Hrs Angina pectoris                                         | Recovered |
| 013-020 1374           | 67 F        | 1               | Dissection, coronary artery                                 | Recovered |
| 013-020 2932           | 58 M        | 1<br>1<br>2     | Bruit<br>Bleeding, postoperative<br>Cardiogenic shock       | Recovered |
| 013-020 2933           | 81 M        | 1               | Dissection, coronary artery                                 | Recovered |
| 013-025 1850           | 78 M        | 2               | Dissection, coronary artery                                 | Recovered |
| 013-026 1992           | 45 M        | 1               | Dissection, coronary artery                                 | Recovered |
| 013-026 3653           | 77 F        | 1               | Dissection, coronary artery                                 | Recovered |
| 013-027 1158           | 58 M        | 1<br>1          | Cardiac tamponade<br>Surgery, heart vessel,<br>complication | Recovered |
| 013-027 3328           | 43 M        | 1               | Occlusion, coronary artery                                  | Recovered |
| 013-030 1445           | 71 F        | 1               | Hemorrhage, retroperitoneal                                 | Recovered |
| 013-030 2094           | 61 F        | 1               | Dissection, coronary artery                                 | Recovered |
| 013-030 2689           | 72 M        | 1               | Occlusion, coronary artery                                  | Recovered |
| 013-031 2742           | 74 M        | 2<br>2          | Agitation<br>Confusion                                      | Recovered |

16.0.3 Subjects In Heparin Group Discontinued' After Clinical AEs

Table 16.0.1.1 Discontinuations for clinical AEs in heparin group from phase III studies (cont).

| Protocol/<br>Subject # | Age/<br>Sex | Day of<br>Onset | Adverse Experience          | Outcome    |
|------------------------|-------------|-----------------|-----------------------------|------------|
| <b>HEPARIN GROUP</b>   |             |                 |                             |            |
| <b>RESTORE TRIAL</b>   |             |                 |                             |            |
| 013-032 2099           | 48 M        | 1               | Dissection, coronary artery | Recovered  |
| 013-032 2328           | 50 F        | 1               | Dissection, coronary artery | Recovered  |
| 013-036 1555           | 74 F        | 1               | Hematoma                    | Recovered  |
| 013-037 1783           | 75 M        | 1               | Hypotension                 | Recovered  |
|                        |             | 1               | Bradycardia                 |            |
| 013-037 3877           | 67 M        | 1               | Dissection, coronary artery | Recovered  |
| 013-039 1334           | 64 M        | 1               | Dissection, coronary artery | Recovered  |
| 013-039 2180           | 67 F        | 1               | Rash                        | Recovered  |
| 013-041 1214           | 77 F        | 1               | Hematoma                    | Recovered  |
|                        |             | 1               | Bleeding, postoperative     |            |
| 013-041 2073           | 73 M        | 1               | Dissection, coronary artery | Recovered  |
| 013-042 1342           | 56 M        | 1               | Dissection, coronary artery | Recovered  |
| 013-045 3276           | 43 M        | 1               | Pain, chest§                | Recovered  |
| 013-046 2141           | 74 F        | 1               | Pain, abdominal             | Recovered  |
| 013-046 2406           | 49 M        | 1               | Dissection, coronary artery | Recovered  |
| 013-048 1230           | 71 M        | 2               | Hemorrhage, gingival        | Recovered  |
|                        |             | 2               | Hematoma                    |            |
| 013-048 2044           | 73 M        | 1               | Dissection, coronary artery | Recovered  |
| 013-050 1488           | 68 F        | 2               | Bleeding, postoperative     | Recovered  |
| 013-051 1053           | 67 F        | 1               | Dissection, coronary artery | Recovered  |
| 013-051 1683           | 69 M        | 1               | Dissection, coronary artery | Recovered  |
| 013-051 1686           | 73 M        | 2               | Drug overdose               | Recovered  |
| 013-052 1703           | 59 M        | 1               | Dissection, coronary artery | Recovered  |
| 013-052 2903           | 64 F        | 2               | Occlusion, arterial         | Recovered  |
| 013-053 1473           | 59 F        | 1               | Dissection, coronary artery | Recovered  |
| 013-053 1948           | 60 M        | 1               | Dissection, coronary artery | Recovered  |
| 013-053 1954           | 71 M        | 1               | Dissection, coronary artery | Recovered  |
| 013-053 2297           | 67 M        | 1               | Dissection, coronary artery | Recovered  |
| 013-056 1173           | 67 F        | 1               | Dissection, coronary artery | Recovered  |
| 013-056 1451           | 50 M        | 1               | Dissection, coronary artery | Recovered  |
| 013-056 1761           | 63 M        | 1               | Surgery                     | Recovered  |
| 013-056 2873           | 77 F        | 1               | Dissection, coronary artery | Recovered  |
| 013-060 1165           | 62 F        | 1               | Dissection, coronary artery | Recovered  |
| 013-061 3063           | 61 M        | 1               | Dissection, coronary artery | Recovered  |
| 013-062 1414           | 71 F        | 2               | Hemorrhage                  | Recovered  |
| 013-062 1604           | 63 F        | 2               | Urticaria                   | Recovered  |
| 013-062 3934           | 68 F        | 1               | Dissection, coronary artery | Recovered  |
| 013-064 1779           | 54 M        | 1               | Dissection, coronary artery | Recovered  |
| 013-069 3369           | 48 M        | 1               | Dissection, coronary artery | Recovered  |
| 013-070 2454           | 65 F        | 2               | Rash                        | Continuing |
|                        |             | 2               | Pruritus                    |            |
| 013-070 2456           | 71 M        | 2               | Renal insufficiency         | Recovered  |
|                        |             | 2               | Respiratory distress        |            |
| 013-071 3901           | 58 M        | 2               | Hemorrhage                  | Recovered  |
|                        |             | 2               | Bleeding, postoperative     |            |
| 013-076 1514           | 62 M        | 1               | Dissection, coronary artery | Recovered  |
| 013-076 1519           | 57 M        | 1               | Hematemesis                 | Recovered  |

16.0.3 Subjects In Heparin Group Discontinued After Clinical AEs

Table 16.0.1.1 Discontinuations for clinical AEs in heparin group from phase III studies (cont):

| Protocol/<br>Subject # | Age/<br>Sex | Day of<br>Onset | Adverse Experience                                                    | Outcome    |
|------------------------|-------------|-----------------|-----------------------------------------------------------------------|------------|
| <b>HEPARIN GROUP</b>   |             |                 |                                                                       |            |
| <b>RESTORE TRIAL</b>   |             |                 |                                                                       |            |
| 013-082 1658           | 61M         | 1<br>1          | Pseudoaneurysm<br>Bleeding, postoperative                             | Recovered  |
| 013-083 1661           | 74 F        | 1               | Hemorrhage                                                            | Recovered  |
| 013-084 3034           | 39 M        | 1               | Dissection, coronary artery                                           | Recovered  |
| 013-088 2513           | 59 M        | 1<br>1          | Paresthesia<br>Paresthesia                                            | Continuing |
| 013-088 2878           | 55 M        | 1               | Dissection, coronary artery                                           | Recovered  |
| 013-088 2881           | 64 M        | 1<br>1          | Anaphylaxis<br>CVA                                                    | Continuing |
| 013-089 2561           | 63 F        | 1               | Dissection, coronary artery                                           | Recovered  |
| 013-090 2417           | 65 M        | 1<br>1          | Bleeding, postoperative<br>Bleeding, postoperative                    | Recovered  |
| 013-091 1743           | 48 M        | 1               | Dissection, coronary artery                                           | Recovered  |
| 013-091 1750           | 66 M        | 2<br>2          | Occlusion, coronary artery<br>Dissection, coronary                    | Recovered  |
| 013-091 2863           | 65 F        | 1               | Dissection, coronary artery                                           | Recovered  |
| 013-093 2017           | 65F         | 1               | Dissection, coronary artery                                           | Recovered  |
| 013-098 2442           | 73 M        | 2               | Confusion                                                             | Recovered  |
| 013-100 4192           | 60 M        | 1               | Dissection, coronary artery                                           | Recovered  |
| 013-100 2055           | 72 M        | 1               | Dissection, coronary artery                                           | Recovered  |
| 013-101 2102           | 48 M        | 1               | Occlusion, coronary artery                                            | Recovered  |
| 013-101 2204           | 51 M        | 2               | Dyspnea                                                               | Recovered  |
| 013-101 2213           | 73 F        | 1<br>1          | Dissection, coronary artery<br>Surgery, heart vessel,<br>complication | Recovered  |
| 013-106 5201           | 41 M        | 1               | Dissection, coronary artery                                           | Recovered  |
| 013-108 5181           | 46 M        | 1               | Dissection, coronary artery                                           | Recovered  |
| 013-110 5045           | 63 M        | 2               | Hrs Hemorrhage,<br>retroperitoneal                                    | Recovered  |
| 013-110 5052           | 55 M        | 1               | Dissection, coronary artery                                           | Recovered  |
| 013-113 2722           | 59 F        | 2               | Occlusion, coronary artery                                            | Recovered  |
| 013-116 5664           | 59 M        | 2               | Dissection, coronary artery                                           | Recovered  |
| 013-116 5667           | 45 M        | 1               | Dissection, coronary artery                                           | Recovered  |
| 013-116 5670           | 47 M        | 1               | Dissection, coronary artery                                           | Recovered  |
| 013-116 5672           | 57 M        | 1               | Dissection, coronary artery                                           | Recovered  |
| 013-119 3648           | 42 M        | 1               | Dissection, coronary artery                                           | Recovered  |
| 013-119 3814           | 57 F        | 2               | Paresthesia                                                           | Recovered  |
| 013-119 3816           | 57 M        | 1               | Occlusion, coronary artery                                            | Recovered  |
| 013-120 3308           | 63 F        | 1               | Dissection, coronary artery                                           | Recovered  |
| 013-120 3663           | 59 M        | 1               | Occlusion, coronary artery                                            | Recovered  |

17.0 Appendix Five: subjects discontinued for laboratory abnormalities

The listing of subjects discontinued for laboratory abnormalities appears below.

17.0.1 Subjects In Tirofiban Group Discontinued After Laboratory AEs

Table 17.0.1.1 Discontinuations for laboratory AEs in the Tirofiban group from the Phase II-III trials<sup>a</sup>.

| Protocol/<br>Subject #  | Age/ Sex | Day of Onset | Adverse Experience                                                       | Lab Value                     |
|-------------------------|----------|--------------|--------------------------------------------------------------------------|-------------------------------|
| <b>TIROFIBAN GROUP</b>  |          |              |                                                                          |                               |
| <b>PRISM-PLUS TRIAL</b> |          |              |                                                                          |                               |
| 006-034 6600            | 68 M     | 2            | Hemoglobin decreased                                                     | 8.0 g/l                       |
| 006-057 6615            | 81 M     | 3            | Platelet count decreased                                                 | 85,000/l                      |
| <b>PRISM TRIAL</b>      |          |              |                                                                          |                               |
| 011-007 1462            | 51 F     | 1            | Platelet count decreased                                                 | 24,000/l                      |
| 011-026 1003            | 74 F     | 1            | Platelet count decreased<br>Hemoglobin decreased<br>Hematocrit decreased | 88,000/l<br>10.5 g/l<br>33.3% |
| 011-079 3752            | 84 F     | 1            | Partial thromboplastin-time increased                                    | 180 secs                      |
| 011-103 3210            | 49 M     | 2            | Platelet count decreased                                                 | 74,000/l                      |
| 011-103 4154            | 63 M     | 3            | Platelet count decreased                                                 | 90,000/l                      |
| 011-123 4460            | 49 M     | 3            | Platelet count decreased                                                 | 94,000/l                      |
| 011-128 3186            | 51 M     | 2            | Partial thromboplastin-time increased                                    | 283 secs                      |
| 011-142 1904            | 41 M     | (2)          | Platelet count decreased                                                 | 77,000/l                      |

a. Data from individual study reports and electronic datasets from NDA 20-912.

17.0.2 Subjects In Tirofiban + Heparin Group Discontinued After Laboratory AEs

Table 17.0.2.1 Discontinuations for laboratory AEs in the Tirofiban + Heparin group from the Phase II-III trials<sup>a</sup>.

| Protocol/<br>Subject #               | Age/ Sex | Day of Onset | Adverse Experience                                                                | Lab Value                                |
|--------------------------------------|----------|--------------|-----------------------------------------------------------------------------------|------------------------------------------|
| <b>TIROFIBAN +<br/>HEPARIN GROUP</b> |          |              |                                                                                   |                                          |
| <b>PRISM-PLUS TRIAL</b>              |          |              |                                                                                   |                                          |
| 006-004 5367                         | 77 M     | 2            | Fecal occult blood                                                                | positive                                 |
| 006-026 5632                         | 66 M     | 3            | Platelet count decreased                                                          | 146,000/l                                |
| 006-032 1027                         | 76 F     | 5            | Hemoglobin decreased                                                              | 7.3 g/l                                  |
| 006-034 6089                         | 64 F     | 4            | Hematuria                                                                         | positive                                 |
| 006-084 7842                         | 49 M     | 1            | Platelet count decreased                                                          | 134,000/l                                |
| <b>RESTORE TRIAL</b>                 |          |              |                                                                                   |                                          |
| 013-009 1564                         | 50 M     | 1            | Thrombocytopenia                                                                  | 85,000/l                                 |
| 013-011 1522                         | 41 M     | 1            | Thrombocytopenia                                                                  | 80,000/l                                 |
| 013-014 3250                         | 73 F     | 1            | Platelet count decreased                                                          | 93,000/l                                 |
| 013-014 3996                         | 75 F     | 1            | Thrombocytopenia                                                                  | 81,000/l                                 |
| 013-027 2504                         | 73 M     | 1<br>1<br>1  | Prothrombin time increased<br>Platelet count decreased<br>Activated PTT increased | 16.8 seconds<br>137,000/l<br>240 seconds |
| 013-080 1924                         | 67 M     | 1            | Thrombocytopenia                                                                  | 51,000/l                                 |
| 013-091 2860                         | 64 M     | 2            | Hematuria                                                                         | Positive                                 |
| 013-106 5212                         | 69 M     | 2            | Thrombocytopenia                                                                  | 85,000/l                                 |
| 013-110 5046                         | 73 M     | 2            | Thrombocytopenia                                                                  | 82,000/l                                 |

a. Data from individual study reports and electronic datasets from NDA 20-912.

17.0.3 Subjects In **Heparin** Group Discontinued After Laboratory AEs

Table 17.0.3.1 Discontinuations for laboratory AEs in the Heparin group from the Phase II-III trials<sup>a</sup>.

| Protocol/<br>Subject #  | Age/ Sex | Day of Onset | Adverse Experience                           | Lab Value      |
|-------------------------|----------|--------------|----------------------------------------------|----------------|
| <b>HEPARIN GROUP</b>    |          |              |                                              |                |
| <b>PRISM-PLUS TRIAL</b> |          |              |                                              |                |
| 006-042 7053            | 44 M     | 3            | Hemoglobin decreased                         | 10.9 g/l       |
| 006-049 6586            | 72 M     | 3            | Hematuria                                    | 4+ positive    |
| 006-050 1031            | 75 F     | 2            | Hemoglobin decreased                         | 9.7 g/l        |
| 006-053 5526            | 55 M     | 1            | Serum creatinine increased                   | 2.8 g/dl       |
| 006-089 7852            | 73 F     | 5            | Hemoglobin decreased<br>hematocrit decreased | 7.4 g/l<br>23% |
| <b>PRISM TRIAL</b>      |          |              |                                              |                |
| 011-024 1769            | 67 F     | 2            | Hemoglobin decreased                         | 10.5 g/l       |
| 011-066 3288            | 66 M     | 2            | Hemoglobin decreased                         | 9.9 g/l        |
| 011-066 3292            | 78 F     | 2            | Hemoglobin decreased                         | 9.9 g/l        |
| 011-178 7529            | 67 F     | 2            | Hemoglobin decreased                         | 10.6 g/l       |
| <b>RESTORE TRIAL</b>    |          |              |                                              |                |
| 013-050 1488            | 68 F     | 2            | Platelet count decreased                     | 133,000/l      |
| 013-109 5100            | 45 M     | 1            | Platelet count decreased                     | 51,000/l       |

a. Data from individual study reports and electronic datasets from NDA 20-912.

## 18.0 Appendix Six: Clinical Adverse Event tables

The tables below summarize the clinical adverse events identified in the overall safety database, as well as in selected sub-groups of the NDA population. The order of the AE tables is as follows:

- A. Overall Adverse event tables from the entire phase II-III database: Nonbleeding AEs  
Overall Adverse Event tables from the entire phase II-III database: Bleeding AEs
- B. Overall Adverse Events grouped according to race of the subjects.
- C. Overall Adverse Events grouped according to gender of the subjects.
- D. Overall Adverse Events grouped according to age of the subjects (<65, ≥65 years of age).
- E. Occurrence of AEs in the phase II-III database, grouped according to presence or absence of hypertension.
- F. Occurrence of AEs in the phase II-III database, grouped according to presence or absence of hypercholesterolemia.
- G. Occurrence of AEs in the phase II-III database, grouped according to presence or absence of diabetes.
- H. Occurrence of AEs in the phase II-III database, for those subjects who received ticlopidine during their respective trials.
- I. Occurrence of AEs in the phase II-III database, for those subjects who received warfarin during their respective trials.
- J. Occurrence of AEs in the phase II-III database, for those subjects who received &blockers during their respective trials.
- K. Occurrence of AEs in the phase II-III database, for those subjects who received calcium channel blockers during their respective trials.
- L. Occurrence of AEs in the phase II-III database, for those subjects who received nitrates blockers during their respective trials.
- M. Occurrence of AEs in the phase II-III database, for those subjects who received non-steroidal anti-inflammatory drugs (NSAIDS) blockers during their respective trials.

### A. Overall Adverse event tables from the entire phase II-III database: Nonbleeding AEs

The adverse experience tables below present the percentages of subjects having at least one adverse event on treatment during the adverse experience reporting period of the respective protocols (nonserious events through 24 hours after drug cessation; serious adverse events through Day 30 after start of study drug). Only those events which occurred at a rate of 21.0% in any of the treatment groups are presented. A subject may be counted more than once if he/she had multiple adverse experiences classified in more than one body system. However, a given patient is counted only once in the overall total and once in any particular body system, regardless of how many clinical adverse experiences were reported in that body system. Similarly, a subject who reported multiple occurrences of the same adverse event appears only once for that particular adverse event.

Adverse events are broken into bleeding and nonbleeding for purposes of review. This comes from the relative incidence of bleeding events in the trials of this NDA. Additionally, as was discussed in section 8.0.4.7 above, the sponsor argues that there is a significant difference in the rates and types of adverse events seen the trials involving pre-specified use of procedures (angioplasty in the RESTORE trial, angiography in the PRISM-PLUS trial). To facilitate this comparison, three 'Heparin' columns will be presented for the adverse events: Heparin/Procedures; Heparin/No procedures; and Total Heparin Alone.

The shaded boxes represents AEs where there is ≥2X difference between one of the two tirofiban groups and either its respective heparin group, or the total heparin group.

18.0 Appendix Six: Clinical Adverse Event tables (cont)

Table 18.0.1 Nonbleeding adverse events in the phase II-III trials of tirofiban from NDA 20-912.

|                                             | Tirofiban + Heparin<br>n=1953 | Heparin Procedures<br>n=1887 | Tirofiban<br>n=2032 | Heparin No Procedures<br>n=1659 | Total Heparin Alone<br>n=3546 |
|---------------------------------------------|-------------------------------|------------------------------|---------------------|---------------------------------|-------------------------------|
| Patients with a nonbleeding clinical AE     | 1545 (79.1%)                  | 1465 (77.6%)                 | 1111 (54.7%)        | 812 (48.9%)                     | 2277 (64.2%)                  |
| Patients without a nonbleeding clinical AE  | 408 (20.9%)                   | 422 (22.4%)                  | 921 (45.3%)         | 847 (51.1%)                     | 1269 (35.8%)                  |
| <b>Body as a whole</b>                      | <b>650 (33.3%)</b>            | <b>597 (31.6%)</b>           | <b>354 (17.4%)</b>  | <b>232 (14.0%)</b>              | <b>829 (23.5%)</b>            |
| Asthenia/fatigue                            | 48 (2.5%)                     | 52 (2.8%)                    | 31 (1.5%)           | 7 (0.4%)                        | 59 (1.7%)                     |
| Death                                       | 39 (2.0%)                     | 47 (2.5%)                    | 61 (3.0%)           | 62 (3.7%)                       | 109 (3.1%)                    |
| Drug overdose                               | 38 (1.9%)                     | 37 (2.0%)                    | 40 (2.0%)           | 36 (2.2%)                       | 73 (2.1%)                     |
| Edema/swelling                              | 31 (1.6%)                     | 27 (1.4%)                    | 24 (1.2%)           | 9 (0.5%)                        | 36 (1.0%)                     |
| Fever                                       | 123 (6.3%)                    | 120 (6.4%)                   | 56 (2.8%)           | 38 (2.3%)                       | 158 (4.5%)                    |
| Hyperthermia                                | 22 (1.1%)                     | 20 (1.1%)                    | 0.4 (0%)            | 0 (0.0%)                        | 20 (0.6%)                     |
| Malaise                                     | 17 (0.9%)                     | 18 (1.0%)                    | 5 (0.2%)            | 3 (0.2%)                        | 21 (0.6%)                     |
| Pain                                        | 23 (1.2%)                     | 26 (1.4%)                    | 16 (0.8%)           | 2 (0.1%)                        | 28 (0.8%)                     |
| Pain, abdominal                             | 102 (5.2%)                    | 86 (4.6%)                    | 60 (3.0%)           | 35 (2.1%)                       | 121 (3.4%)                    |
| Pain, chest                                 | 162 (8.3%)                    | 172 (9.1%)                   | 46 (2.3%)           | 36 (2.2%)                       | 208 (5.9%)                    |
| Pain, pelvic                                | 115 (5.9%)                    | 90 (4.8%)                    | 15 (0.7%)           | 4 (0.2%)                        | 94 (2.7%)                     |
| Reaction, vasovagal                         | 40 (2.0%)                     | 20 (1.1%)                    | 12 (0.6%)           | 4 (0.2%)                        | 24 (0.7%)                     |
| <b>Cardiovascular System</b>                | <b>664 (34.0%)</b>            | <b>644 (34.1%)</b>           | <b>468 (23.0%)</b>  | <b>325 (19.6%)</b>              | <b>969 (27.3%)</b>            |
| Angina, pectoris                            | 26 (1.3%)                     | 27 (1.4%)                    | 9 (0.4%)            | 11 (0.7%)                       | 38 (1.1%)                     |
| Angina, unstable                            | 27 (1.4%)                     | 21 (1.1%)                    | 71 (3.5%)           | 57 (3.4%)                       | 78 (2.2%)                     |
| Atrial fibrillation                         | 18 (0.9%)                     | 19 (1.0%)                    | 14 (0.7%)           | 15 (0.9%)                       | 34 (1.0%)                     |
| Bradycardia                                 | 73 (3.7%)                     | 52 (2.8%)                    | 20 (1.0%)           | 23 (1.4%)                       | 75 (2.1%)                     |
| Dissection, coronary artery                 | 88 (4.5%)                     | 83 (4.4%)                    | 4 (0.2%)            | 3 (0.2%)                        | 86 (2.4%)                     |
| Heart failure                               | 33 (1.7%)                     | 35 (1.9%)                    | 38 (1.9%)           | 46 (2.8%)                       | 81 (2.3%)                     |
| Hypertension                                | 22 (1.1%)                     | 19 (1.0%)                    | 9 (0.4%)            | 4 (0.2%)                        | 23 (0.7%)                     |
| Hypotension                                 | 150 (7.7%)                    | 15 (0.8%)                    | 74 (3.6%)           | 39 (2.4%)                       | 192 (5.4%)                    |
| Infused vein complication                   | 40 (2.0%)                     | 41 (2.2%)                    | 46 (2.3%)           | 16 (1.0%)                       | 57 (1.6%)                     |
| Pain, catheter, cardiac                     | 16 (0.8%)                     | 24 (1.3%)                    | 6 (0.3%)            | 1 (0.1%)                        | 25 (0.7%)                     |
| Peripheral pulse, decreased                 | 20 (1.0%)                     | 12 (0.6%)                    | 7 (0.3%)            | 1 (0.1%)                        | 13 (0.4%)                     |
| Phlebitis/thrombophlebitis                  | 10 (0.5%)                     | 13 (0.7%)                    | 23 (1.1%)           | 15 (0.9%)                       | 28 (0.8%)                     |
| Premature ventricular contractions          | 32 (1.6%)                     | 40 (2.1%)                    | 17 (0.8%)           | 10 (0.6%)                       | 50 (1.4%)                     |
| Shock, cardiogenic                          | 20 (1.0%)                     | 16 (0.8%)                    | 28 (1.4%)           | 18 (1.1%)                       | 34 (1.0%)                     |
| Ventricular tachycardia                     | 36 (1.8%)                     | 58 (3.1%)                    | 24 (1.2%)           | 10 (0.6%)                       | 68 (1.9%)                     |
| <b>Digestive System</b>                     | <b>470 (24.1%)</b>            | <b>448 (23.7%)</b>           | <b>270 (13.3%)</b>  | <b>168 (10.1%)</b>              | <b>616 (17.4%)</b>            |
| Acid regurgitation                          | 26 (1.3%)                     | 26 (1.4%)                    | 11 (0.5%)           | 6 (0.4%)                        | 32 (0.9%)                     |
| Constipation                                | 103 (5.3%)                    | 93 (4.9%)                    | 85 (4.2%)           | 39 (2.4%)                       | 132 (3.7%)                    |
| Diarrhea                                    | 28 (1.4%)                     | 31 (1.6%)                    | 20 (1.0%)           | 15 (0.9%)                       | 46 (1.3%)                     |
| Dyspepsia                                   | 40 (2.0%)                     | 41 (2.2%)                    | 26 (1.3%)           | 22 (1.3%)                       | 63 (1.8%)                     |
| Nausea                                      | 226 (11.6%)                   | 238 (12.6%)                  | 96 (4.7%)           | 72 (4.3%)                       | 310 (8.7%)                    |
| Vomiting                                    | 106 (5.4%)                    | 101 (5.4%)                   | 42 (2.1%)           | 25 (1.5%)                       | 126 (3.6%)                    |
| <b>Endocrine System</b>                     | <b>6 (0.3%)</b>               | <b>0 (0.0%)</b>              | <b>4 (0.2%)</b>     | <b>2 (0.1%)</b>                 | <b>2 (&lt;0.1%)</b>           |
| <b>Hemic and Lymphatic System</b>           | <b>20 (1.0%)</b>              | <b>12 (0.6%)</b>             | <b>18 (0.9%)</b>    | <b>6 (0.4%)</b>                 | <b>18 (0.5%)</b>              |
| <b>Metabolic/Nutritional/Immune Systems</b> | <b>24 (1.2%)</b>              | <b>31 (1.6%)</b>             | <b>19 (0.9%)</b>    | <b>9 (0.5%)</b>                 | <b>40 (1.1%)</b>              |
| <b>Musculoskeletal System</b>               | <b>554 (28.4%)</b>            | <b>540 (28.6%)</b>           | <b>145 (7.1%)</b>   | <b>77 (4.6%)</b>                | <b>617 (17.4%)</b>            |
| Pain, arm                                   | 35 (1.8%)                     | 28 (1.5%)                    | 7 (0.3%)            | 4 (0.2%)                        | 32 (0.9%)                     |
| Pain, back                                  | 443 (22.7%)                   | 425 (22.5%)                  | 68 (3.3%)           | 35 (2.1%)                       | 460 (13.0%)                   |
| Pain, leg                                   | 50 (2.6%)                     | 32 (1.7%)                    | 11 (0.5%)           | 8 (0.5%)                        | 40 (1.1%)                     |
| Pain, shoulder                              | 26 (1.3%)                     | 34 (1.8%)                    | 17 (0.8%)           | 9 (0.5%)                        | 43 (1.2%)                     |

18.0 Appendix Six: Clinical Adverse Event tables (cont)

Table 18.0.1 Nonbleeding adverse events in the phase II-III trials of tirofiban from NDA 20-912<sup>a</sup>.

|                                       | Tirofiban + Heparin<br>n=1953 | Heparin/<br>Procedures<br>n=1887 | Tirofiban<br>n=2032 | Heparin/<br>No Procedures<br>n=1659 | Total Heparin<br>Alone<br>n=3546 |
|---------------------------------------|-------------------------------|----------------------------------|---------------------|-------------------------------------|----------------------------------|
| <b>Nervous System and Psychiatric</b> | 642 (32.9%)                   | 645 (34.2%)                      | 512 (25.2%)         | 353 (21.3%)                         | 1007 (28.4%)                     |
| Agitation                             | 30 (1.5%)                     | 32 (1.7%)                        | 12 (0.6%)           | 5 (0.3%)                            | 37 (1.0%)                        |
| Anxiety                               | 127 (6.5%)                    | 148 (7.8%)                       | 78 (3.8%)           | 48 (2.9%)                           | 196 (5.5%)                       |
| Anxiety disorder                      | 26 (1.3%)                     | 21 (1.1%)                        | 20 (1.0%)           | 2 (0.1%)                            | 23 (0.6%)                        |
| Confusion                             | 37 (1.9%)                     | 37 (2.0%)                        | 17 (0.8%)           | 14 (0.8%)                           | 51 (1.4%)                        |
| Dizziness                             | 52 (2.7%)                     | 41 (2.2%)                        | 41 (2.0%)           | 15 (0.9%)                           | 56 (1.6%)                        |
| Headache                              | 336 (17.2%)                   | 367 (19.4%)                      | 323 (15.9%)         | 237 (14.3%)                         | 604 (17.0%)                      |
| Insomnia                              | 130 (6.7%)                    | 129 (6.8%)                       | 95 (4.7%)           | 62 (3.7%)                           | 191 (5.4%)                       |
| Nervousness                           | 41 (2.1%)                     | 32 (1.7%)                        | 8 (0.4%)            | 5 (0.3%)                            | 37 (1.0%)                        |
| Somnolence                            | 21 (1.1%)                     | 29 (1.5%)                        | 15 (0.7%)           | 2 (0.1%)                            | 31 (0.9%)                        |
| <b>Respiratory System</b>             | 214 (11.0%)                   | 227 (12.0%)                      | 162 (8.0%)          | 126 (7.6%)                          | 353 (10.0%)                      |
| Cough                                 | 33 (1.7%)                     | 31 (1.6%)                        | 17 (0.8%)           | 8 (0.5%)                            | 39 (1.1%)                        |
| Dyspnea                               | 46 (2.4%)                     | 49 (2.6%)                        | 26 (1.3%)           | 18 (1.1%)                           | 67 (1.9%)                        |
| Edema, pulmonary                      | 16 (0.8%)                     | 18 (1.0%)                        | 26 (1.3%)           | 24 (1.4%)                           | 42 (1.2%)                        |
| Rales/rhonchi                         | 46 (2.4%)                     | 54 (2.9%)                        | 31 (1.5%)           | 23 (1.4%)                           | 77 (2.2%)                        |
| <b>Skin and Skin Appendage</b>        | 127 (6.5%)                    | 117 (6.2%)                       | 91 (4.5%)           | 45 (2.7%)                           | 162 (4.6%)                       |
| Rash                                  | 20 (1.0%)                     | 17 (0.9%)                        | 11 (0.5%)           | 9 (0.5%)                            | 26 (0.7%)                        |
| Sweating                              | 34 (1.7%)                     | 24 (1.3%)                        | 12 (0.6%)           | 2 (0.1%)                            | 26 (0.7%)                        |
| <b>Special Senses</b>                 | 20 (1.0%)                     | 25 (1.3%)                        | 16 (0.8%)           | 6 (0.4%)                            | 31 (0.9%)                        |
| <b>Urogenital</b>                     | 123 (6.3%)                    | 122 (6.5%)                       | 71 (3.5%)           | 49 (3.0%)                           | 171 (4.8%)                       |
| Infection urinary tract               | 38 (1.9%)                     | 34 (1.8%)                        | 24 (1.2%)           | 20 (1.2%)                           | 54 (1.5%)                        |
| Urinary retention                     | 10 (0.5%)                     | 19 (1.0%)                        | 6 (0.3%)            | 1 (0.1%)                            | 20 (0.6%)                        |

<sup>a</sup> Data from NDA volume 1.2, Table C-37 and electronic datasets.

18.0 Appendix Six: Clinical Adverse Event tables (cont)

**A. Overall Adverse Event tables from the entire phase II-III database: Bleeding AEs**

The table below shows the percentage of subjects with clinical bleeding adverse experiences.

Table 18.0.2 Bleeding adverse events in the phase II-III trials of tirofiban from NDA 20-912<sup>a</sup>.

|                                       | Tirofiban<br>+ Heparin<br>n=1953 | Heparin/<br>Procedures<br>n=1887 | Tirofiban<br>n=2032 | Heparin/<br>No Procedures<br>n=1659 | Total Heparin<br>Alone<br>n=3546 |
|---------------------------------------|----------------------------------|----------------------------------|---------------------|-------------------------------------|----------------------------------|
| Patients with bleeding clinical AE    | 1021 (52.3%)                     | 733 (38.8%)                      | 424 (20.9%)         | 143 (8.6%)                          | 876 (24.7%)                      |
| Patients without bleeding clinical AE | 932 (47.7%)                      | 1154 (61.2%)                     | 1608 (79.1%)        | 1516 (91.4%)                        | 2670 (75.2%)                     |
| <b>Body as a whole</b>                | <b>1 (0.1%)</b>                  | <b>1 (0.1%)</b>                  | <b>10 (0.5%)</b>    | <b>9 (0.5%)</b>                     | <b>10 (0.3%)</b>                 |
| <b>Cardiovascular System</b>          | <b>844 (43.2%)</b>               | <b>616 (32.6%)</b>               | <b>245 (12.1%)</b>  | <b>86 (5.2%)</b>                    | <b>702 (19.8%)</b>               |
| Bleeding, postoperative               | 659 (33.7%)                      | 468 (24.8%)                      | 139 (6.8%)          | 34 (2.0%)                           | 502 (14.1%)                      |
| Extravasation                         | 8 (0.4%)                         | 3 (0.2%)                         | 13 (0.6%)           | 4 (0.2%)                            | 7 (<0.1%)                        |
| Hematoma                              | 206 (10.5%)                      | 125 (6.6%)                       | 63 (3.1%)           | 26 (1.6%)                           | 151 (4.2%)                       |
| Hemorrhage                            | 24 (1.2%)                        | 39 (2.1%)                        | 11 (0.5%)           | 3 (0.2%)                            | 42 (1.2%)                        |
| Hemorrhage, I.V. site                 | 105 (5.4%)                       | 77 (4.1%)                        | 61 (3.0%)           | 20 (1.2%)                           | 97 (2.7%)                        |
| <b>Digestive System</b>               | <b>96 (4.9%)</b>                 | <b>29 (1.5%)</b>                 | <b>53 (2.6%)</b>    | <b>13 (0.8%)</b>                    | <b>42 (1.2%)</b>                 |
| Hematemesis                           | 17 (0.9%)                        | 6 (0.3%)                         | 4 (0.2%)            | 0 (0.0%)                            | 6 (0.2%)                         |
| Hemorrhage, gastrointestinal          | 18 (0.9%)                        | 4 (0.2%)                         | 11 (0.5%)           | 6 (0.4%)                            | 10 (0.3%)                        |
| Hemorrhage, gingival                  | 19 (1.0%)                        | 3 (0.2%)                         | 11 (0.5%)           | 3 (0.2%)                            | 6 (0.2%)                         |
| Hemorrhage, oral                      | 28 (1.4%)                        | 5 (0.3%)                         | 8 (0.4%)            | 0 (0.0%)                            | 5 (0.2%)                         |
| <b>Hemic and Lymphatic System</b>     | <b>4 (0.2%)</b>                  | <b>1 (0.1%)</b>                  | <b>5 (0.2%)</b>     | <b>0 (0.0%)</b>                     | <b>1 (&lt;0.1%)</b>              |
| <b>Respiratory System</b>             | <b>125 (6.4%)</b>                | <b>33 (1.7%)</b>                 | <b>143 (7.0%)</b>   | <b>21 (1.3%)</b>                    | <b>54 (1.5%)</b>                 |
| Epistaxis                             | 109 (5.6%)                       | 20 (1.1%)                        | 130 (6.4%)          | 18 (1.1%)                           | 38 (1.1%)                        |
| Hemoptysis                            | 23 (1.2%)                        | 11 (0.6%)                        | 18 (0.9%)           | 3 (0.2%)                            | 14 (0.4%)                        |
| <b>Skin and Skin Appendage</b>        | <b>222 (11.4%)</b>               | <b>154 (8.2%)</b>                | <b>43 (2.1%)</b>    | <b>5 (0.3%)</b>                     | <b>159 (4.5%)</b>                |
| Ecchymosis                            | 217 (11.1%)                      | 153 (8.1%)                       | 40 (2.0%)           | 5 (0.3%)                            | 158 (4.5%)                       |
| <b>Special Senses</b>                 | <b>3 (0.2%)</b>                  | <b>0 (0.0%)</b>                  | <b>3 (0.1%)</b>     | <b>2 (0.1%)</b>                     | <b>2 (&lt;0.1%)</b>              |
| Urogenital                            | 73 (3.7%)                        | 49 (2.6%)                        | 29 (1.4%)           | 18 (1.1%)                           | 67 (1.9%)                        |
| Hematuria                             | 67 (3.4%)                        | 42 (2.2%)                        | 26 (1.3%)           | 17 (1.0%)                           | 59 (1.7%)                        |

a. Data from NDA volume 1.2, Table C-39 and electronic datasets.

18.0 Appendix Six: **Clinical** Adverse Event tables (cont)

**B. Overall Adverse Events grouped according to race of the subjects**

The table below shows the percentage of subjects with clinical adverse experiences grouped according to race, occurring in 22.0% of subjects in any of the age subgroups/treatment group categories. Due to the many comparisons, the table is broken into two parts: the first part displays the clinical AE profile for the tirofiban plus heparin and heparin/procedure groups only; the second part summarizes the clinical AEs in the tirofiban alone and heparin/no procedure groups.

Table 18.0.3 Adverse events in the phase II-III tirofiban database according to race of subject'. Data shown for subjects in Tirofiban + Heparin and Heparin/Procedures groups'.

|                                      | Tirofiban + Heparin |                    |               |               |               | Heparin/Procedures  |               |               |               |               |
|--------------------------------------|---------------------|--------------------|---------------|---------------|---------------|---------------------|---------------|---------------|---------------|---------------|
|                                      | White<br>N=<br>1693 | Black<br>N=<br>117 | Asian<br>N=10 | Hisp.<br>N=88 | Other<br>N=45 | White<br>N=<br>1654 | Black<br>N=81 | Asian<br>N=19 | Hisp.<br>N=79 | Other<br>N=54 |
| % subjects with clinical AE          | 67.4                | 84.6               | 100.0         | 69.3          | 82.2          | 84.1                | 84.0          | 84.2          | 63.3          | 68.5          |
| % of subjects without clinical AE    | 12.6                | 15.4               | 0.0           | 30.7          | 17.8          | 15.9                | 16.0          | 15.8          | 36.7          | 31.5          |
| Body as a Whole/Site Unspecified     | 34.0                | 35.9               | 50.0          | 23.9          | 22.2          | 32.2                | 33.3          | 57.9          | 21.5          | 18.0          |
| Asthenia/fatigue                     | 2.6                 | 0.9                | 20.0          | 1.1           | 0.0           | 3.1                 | 1.2           | 0.0           | 0.0           | 0.0           |
| Death                                | 2.1                 | 0.0                | 0.0           | 3.4           | 0.0           | 2.2                 | 2.5           | 0.0           | 5.1           | 7.4           |
| Drug overdose                        | 2.1                 | 2.6                | 0.0           | 0.0           | 0.0           | 1.8                 | 3.7           | 10.5          | 3.8           | 0.0           |
| Edema/swelling                       | 1.7                 | 1.7                | 10.0          | 0.0           | 0.0           | 1.5                 | 0.0           | 0.0           | 1.3           | 1.9           |
| Fever                                | 6.2                 | 10.3               | 0.0           | 3.4           | 6.7           | 6.4                 | 7.4           | 15.8          | 2.5           | 5.6           |
| Pain, abdominal                      | 5.6                 | 3.4                | 0.0           | 3.4           | 2.2           | 4.7                 | 7.4           | 5.3           | 2.5           | 0.0           |
| Pain, chest                          | 8.0                 | 13.7               | 20.0          | 8.0           | 4.4           | 9.1                 | 13.6          | 26.3          | 6.3           | 0.0           |
| Pain, pelvic                         | 5.4                 | 12.8               | 20.0          | 4.5           | 6.7           | 5.0                 | 6.2           | 0.0           | 1.3           | 1.9           |
| Cardiovascular System                | 61.5                | 47.0               | 70.0          | 36.4          | 53.3          | 54.4                | 46.9          | 57.9          | 31.6          | 46.3          |
| Angina, unstable                     | 1.4                 | 0.9                | 0.0           | 0.0           | 6.7           | 1.0                 | 1.2           | 0.0           | 1.3           | 3.7           |
| Bleeding, postoperative              | 35.3                | 28.2               | 40.0          | 21.6          | 13.3          | 26.1                | 24.7          | 26.3          | 8.9           | 7.4           |
| Bradycardia                          | 4.0                 | 2.6                | 0.0           | 0.0           | 6.7           | 2.6                 | 3.7           | 10.5          | 3.8           | 1.9           |
| Dissection, coronary artery          | 4.4                 | 5.1                | 20.0          | 4.5           | 2.2           | 4.7                 | 2.5           | 0.0           | 1.3           | 3.7           |
| Heart failure                        | 1.7                 | 2.6                | 0.0           | 1.1           | 2.2           | 1.8                 | 0.0           | 0.0           | 1.3           | 7.4           |
| Hematoma                             | 10.9                | 8.5                | 30.0          | 2.3           | 13.3          | 6.8                 | 7.4           | 0.0           | 5.1           | 5.6           |
| Hemorrhage                           | 1.2                 | 1.7                | 0.0           | 1.1           | 0.0           | 1.8                 | 7.4           | 5.3           | 2.5           | 0.0           |
| Hemorrhage, I.V. site                | 5.7                 | 3.4                | 0.0           | 3.4           | 4.4           | 4.4                 | 1.2           | 10.5          | 0.0           | 1.9           |
| Hypotension                          | 8.4                 | 3.4                | 0.0           | 1.1           | 6.7           | 8.7                 | 6.2           | 0.0           | 2.5           | 3.7           |
| Premature ventricular contraction    | 1.5                 | 2.6                | 0.0           | 1.1           | 6.7           | 2.2                 | 1.2           | 0.0           | 1.3           | 3.7           |
| Ventricular tachycardia              | 1.9                 | 2.6                | 0.0           | 1.1           | 0.0           | 3.0                 | 3.7           | 10.5          | 3.8           | 0.0           |
| Digestive System                     | 27.8                | 22.2               | 40.0          | 18.2          | 20.0          | 25.1                | 21.0          | 26.3          | 21.5          | 22.2          |
| Constipation                         | 5.5                 | 3.4                | 0.0           | 6.8           | 0.0           | 5.1                 | 3.7           | 5.3           | 5.1           | 1.9           |
| Diarrhea                             | 1.4                 | 0.9                | 20.0          | 0.0           | 2.2           | 1.6                 | 3.7           | 5.3           | 0.0           | 0.0           |
| Nausea                               | 12.1                | 11.1               | 10.0          | 6.8           | 2.2           | 13.1                | 9.9           | 10.5          | 5.1           | 14.8          |
| Vomiting                             | 5.6                 | 4.3                | 10.0          | 3.4           | 6.7           | 5.1                 | 4.9           | 5.3           | 8.9           | 7.4           |
| Endocrine System                     | 0.4                 | 0.0                | 0.0           | 0.0           | 0.0           | 0.0                 | 0.0           | 0.0           | 0.0           | 0.0           |
| Hemic and Lymphatic System           | 1.2                 | 0.9                | 0.0           | 2.3           | 0.0           | 0.7                 | 0.0           | 0.0           | 1.3           | 0.0           |
| Metabolic/Nutritional/Immune Systems | 1.0                 | 1.7                | 0.0           | 4.5           | 2.2           | 1.6                 | 1.2           | 0.0           | 3.8           | 1.9           |
| Musculoskeletal System               | 30.0                | 23.1               | 20.0          | 14.8          | 8.9           | 30.6                | 29.6          | 15.8          | 2.5           | 9.3           |
| Pain, back                           | 24.2                | 18.8               | 20.0          | 9.1           | 4.4           | 24.2                | 22.2          | 5.3           | 2.5           | 5.6           |
| Nervous System and Psychiatric       | 33.6                | 31.6               | 20.0          | 25.0          | 26.7          | 35.3                | 24.7          | 21.1          | 27.8          | 27.8          |
| Anxiety                              | 6.6                 | 5.1                | 0.0           | 6.8           | 6.7           | 8.5                 | 1.2           | 10.5          | 6.3           | 0.0           |
| Headache                             | 17.5                | 14.5               | 20.0          | 13.6          | 20.0          | 19.6                | 13.6          | 10.5          | 20.3          | 24.1          |
| Insomnia                             | 6.9                 | 6.0                | 0.0           | 8.0           | 0.0           | 7.2                 | 6.2           | 0.0           | 5.1           | 1.9           |
| Respiratory System                   | 16.5                | 12.8               | 20.0          | 9.1           | 11.1          | 13.7                | 6.2           | 10.5          | 8.9           | 11.1          |
| Epistaxis                            | 5.8                 | 5.1                | 10.0          | 2.3           | 4.4           | 1.1                 | 0.0           | 0.0           | 2.5           | 0.0           |
| Rales/rhonchi                        | 2.6                 | 0.9                | 0.0           | 1.1           | 0.0           | 2.8                 | 2.5           | 5.3           | 1.3           | 5.6           |

18.0 Appendix Six: Clinical Adverse Event tables (cont)

Table 18.0.3 Adverse events in the phase II-III tirofiban database according to race of subject". Data shown for subjects in Tirofiban + Heparin and Heparin/Procedures groups (cont)<sup>a</sup>.

|                                | Tirofiban + Heparin |                    |               |                  |               | Heparin/Procedures  |               |               |                  |               |
|--------------------------------|---------------------|--------------------|---------------|------------------|---------------|---------------------|---------------|---------------|------------------|---------------|
|                                | White<br>N=<br>1693 | Black<br>N=<br>117 | Asian<br>N=10 | Hispanic<br>N=88 | Other<br>N=45 | White<br>N=<br>1654 | Black<br>N=81 | Asian<br>N=19 | Hispanic<br>N=79 | Other<br>N=54 |
| <b>Skin and Skin Appendage</b> | 18.4                | 9.4                | 10.0          | 10.2             | 2.2           | 14.5                | 8.6           | 10.5          | 2.5              | 3.7           |
| Dermatitis, contact            | 0.0                 | 0.0                | 0.0           | 0.0              | 0.0           | 0.0                 | 0.0           | 10.5          | 0.0              |               |
| Ecchymosis                     | 12.0                | 6.0                | 10.0          | 5.7              | 0.0           | 8.9                 | 6.2           | 0.0           | 0.0              | 1.9           |
| <b>Special Senses</b>          | 1.3                 | 0.0                | 0.0           | 1.1              | 0.0           | 1.3                 | 2.5           | 5.3           | 1.3              | 0.0           |
| <b>Urogenital</b>              | 9.1                 | 12.0               | 10.0          | 4.5              | 8.9           | 8.3                 | 11.1          | 10.5          | 7.6              | 7.4           |
| Hematuria                      | 3.4                 | 3.4                | 10.0          | 2.3              | 6.7           | 2.2                 | 3.7           | 0.0           | 2.5              | 0.0           |
| Infection, urinary tract       | 1.8                 | 4.3                | 0.0           | 2.3              | 2.2           | 1.5                 | 4.9           | 10.5          | 1.3              | 5.6           |

a. Data from NDA volume 1.37, table D-80.

The second part of the adverse events table, grouped according to race, summarizes the clinical AEs in the tirofiban alone and heparin/no procedure groups.

Table 18.0.4 Adverse events in the phase II-III tirofiban database according to race of subject".

|                                                | Tirofiban           |               |               |                  |               | Heparin/No Procedure |               |               |                  |               |
|------------------------------------------------|---------------------|---------------|---------------|------------------|---------------|----------------------|---------------|---------------|------------------|---------------|
|                                                | White<br>N=<br>1727 | Black<br>N=98 | Asian<br>N=32 | Hispanic<br>N=98 | Other<br>N=77 | White<br>N=<br>1395  | Black<br>N=73 | Asian<br>N=39 | Hispanic<br>N=88 | Other<br>N=64 |
| <b>Percent of subjects with clinical AE</b>    | 59.7                | 69.4          | 62.5          | 45.9             | 46.8          | 52.5                 | 60.3          | 48.7          | 43.2             | 34.4          |
| <b>Percent of subjects without clinical AE</b> | 40.3                | 30.6          | 37.5          | 54.1             | 53.2          | 47.5                 | 39.7          | 51.3          | 56.8             | 65.6          |
| <b>Body as a Whole/Site Unspecified</b>        | 18.4                | 23.5          | 12.5          | 10.2             | 10.4          | 14.6                 | 15.1          | 17.9          | 15.9             | 9.4           |
| <b>Death</b>                                   | 2.8                 | 6.1           | 3.1           | 4.1              | 1.3           | 3.7                  | 1.4           | 2.6           | 6.8              | 4.7           |
| Drug overdose                                  | 2.1                 | 2.0           | 3.1           | 0.0              | 0.0           | 2.2                  | 2.7           | 5.1           | 1.1              | 0.0           |
| Fever                                          | 2.7                 | 5.1           | 0.0           | 2.0              | 2.6           | 2.2                  | 4.1           | 7.7           | 2.3              | 0.0           |
| Pain, abdominal                                | 3.1                 | 5.1           | 0.0           | 0.0              | 2.6           | 2.2                  | 1.4           | 5.1           | 2.3              | 0.0           |
| Pain, chest                                    | 2.3                 | 2.0           | 3.1           | 1.0              | 2.6           | 2.2                  | 1.4           | 0.0           | 2.3              | 3.1           |
| <b>Cardiovascular System</b>                   | 31.2                | 24.5          | 31.3          | 15.3             | 22.1          | 23.3                 | 27.4          | 23.1          | 20.5             | 14.1          |
| Bleeding, postoperative                        | 7.5                 | 4.1           | 6.3           | 3.1              | 1.3           | 2.2                  | 2.7           | 2.6           | 1.1              | 0.0           |
| Heart failure                                  | 2.0                 | 1.0           | 3.1           | 1.0              | 1.3           | 3.0                  | 1.4           | 5.1           | 1.1              | 0.0           |
| Hematoma                                       | 3.6                 | 0.0           | 0.0           | 0.0              | 0.0           | 1.6                  | 2.7           | 0.0           | 1.1              | 0.0           |
| Hemorrhage, I.V. site                          | 3.2                 | 2.0           | 0.0           | 2.0              | 1.3           | 1.0                  | 1.4           | 5.1           | 2.3              | 1.6           |
| Hypotension                                    | 3.8                 | 4.1           | 9.4           | 1.0              | 0.0           | 2.4                  | 1.4           | 0.0           | 4.5              | 0.0           |
| <b>Digestive System</b>                        | 14.8                | 24.5          | 25.0          | 17.3             | 7.8           | 11.4                 | 4.1           | 7.7           | 9.1              | 7.8           |
| Constipation                                   | 4.3                 | 8.2           | 0.0           | 3.1              | 0.0           | 2.4                  | 4.1           | 5.1           | 1.1              | 0.0           |
| Hemorrhage, gingival                           | 0.5                 | 0.0           | 6.3           | 1.0              | 0.0           | 0.1                  | 0.0           | 0.0           | 0.0              | 1.6           |
| Nausea                                         | 4.5                 | 5.1           | 15.6          | 5.1              | 3.9           | 5.0                  | 0.0           | 0.0           | 2.3              | 0.0           |
| Vomiting                                       | 2.0                 | 2.0           | 9.4           | 2.0              | 1.3           | 1.7                  | 0.0           | 0.0           | 1.1              | 0.0           |
| <b>Endocrine System</b>                        | 0.2                 | 0.0           | 0.0           | 0.0              | 0.0           | 0.1                  | 0.0           | 0.0           | 0.0              | 0.0           |
| <b>Hemic and Lymphatic System</b>              | 0.9                 | 1.0           | 3.1           | 4.1              | 1.3           | 0.4                  | 0.0           | 2.6           | 0.0              | 0.0           |
| <b>Metabolic/Nutritional/Immune</b>            | 1.0                 | 0.0           | 0.0           | 0.0              | 1.3           | 0.5                  | 1.4           | 0.0           | 0.0              | 1.6           |
| Musculoskeletal System                         | 7.4                 | 10.2          | 3.1           | 6.1              | 0.0           | 4.7                  | 5.5           | 5.1           | 2.3              | 4.7           |
| Pain, back                                     | 3.5                 | 5.1           | 3.1           | 2.0              | 0.0           | 2.2                  | 2.7           | 0.0           | 1.1              | 1.6           |
| <b>Nervous System and Psychiatric</b>          | 25.2                | 39.8          | 21.9          | 19.4             | 15.6          | 21.4                 | 32.9          | 15.4          | 14.8             | 17.2          |
| Anxiety                                        | 4.3                 | 2.0           | 3.1           | 0.0              | 0.0           | 3.3                  | 1.4           | 2.6           | 0.0              | 0.0           |
| Dizziness                                      | 2.0                 | 4.1           | 3.1           | 1.0              | 0.0           | 0.7                  | 5.5           | 0.0           | 0.0              | 1.6           |
| Headache                                       | 15.5                | 28.6          | 12.5          | 13.3             | 14.3          | 13.8                 | 26.0          | 12.8          | 11.4             | 15.6          |
| Insomnia                                       | 4.6                 | 8.2           | 3.1           | 6.1              | 1.3           | 3.7                  | 9.6           | 2.6           | 1.1              | 1.6           |
| <b>Respiratory System</b>                      | 14.0                | 15.3          | 12.5          | 9.2              | 13.0          | 9.0                  | 9.6           | 5.1           | 10.2             | 3.1           |
| Epistaxis                                      | 6.3                 | 7.1           | 3.1           | 6.1              | 10.4          | 1.1                  | 1.4           | 0.0           | 1.1              | 1.6           |
| <b>Skin and Skin Appendage</b>                 | 6.7                 | 5.1           | 0.0           | 2.0              | 5.2           | 3.1                  | 6.8           | 5.1           | 0.0              | 0.0           |
| Ecchymosis                                     | 2.3                 | 1.0           | 0.0           | 0.0              | 0.0           | 0.4                  | 0.0           | 0.0           | 0.0              | 0.0           |
| <b>Special Senses</b>                          | 1.0                 | 2.0           | 0.0           | 0.0              | 0.0           | 0.5                  | 0.0           | 0.0           | 1.1              | 0.0           |
| <b>Urogenital</b>                              | 5.0                 | 4.1           | 0.0           | 2.0              | 3.9           | 3.8                  | 12.3          | 0.0           | 3.4              | 0.0           |
| Infection, urinary tract                       | 1.2                 | 2.0           | 0.0           | 1.0              | 1.3           | 1.0                  | 6.8           | 0.0           | 1.1              | 0.0           |

a. Data from NDA volume 1.37, table D-80.

18.0 Appendix Six: Clinical Adverse Event tables (cont)

C. Overall Adverse Events grouped according to gender of the subjects

The table below shows the percentage of subjects with clinical adverse experiences grouped according to gender, occurring in 22.0% of subjects in any of the age subgroups/treatment group categories.

Table 18.0.5 Adverse events in the phase II-III tirofiban database according to sex of subject<sup>a</sup>.

|                                                | Tirofiban + Heparin |                      | Heparin/ Procedures |                      | Tirofiban           |                      | Heparin/ No Procedures |                      |
|------------------------------------------------|---------------------|----------------------|---------------------|----------------------|---------------------|----------------------|------------------------|----------------------|
|                                                | N=1384<br>Male<br>% | N=569<br>Female<br>% | N=1342<br>Male<br>% | N=545<br>Female<br>% | N=1368<br>Male<br>% | N=664<br>Female<br>% | N=1146<br>Male<br>%    | N=513<br>Female<br>% |
| <b>Percent of subjects with clinical AE</b>    | <b>84.3</b>         | <b>91.4</b>          | <b>81.1</b>         | <b>87.0</b>          | <b>55.7</b>         | <b>66.1</b>          | <b>48.8</b>            | <b>57.9</b>          |
| <b>Percent of subjects without clinical AE</b> | <b>15.7</b>         | <b>8.6</b>           | <b>18.9</b>         | <b>13.0</b>          | <b>44.3</b>         | <b>33.9</b>          | <b>51.2</b>            | <b>42.1</b>          |
| Body as a Whole/Site Unspecified               | 31.2                | 38.8                 | 30.3                | 35.0                 | 15.9                | 22.0                 | 14.4                   | 14.8                 |
| Asthenia/fatigue                               | 2.0                 | 3.7                  | 2.3                 | 3.9                  | 1.2                 | 2.3                  | 0.5                    | 0.2                  |
| Death                                          | 1.7                 | 2.6                  | 2.1                 | 3.5                  | 2.4                 | 4.2                  | 3.8                    | 3.7                  |
| Drug overdose                                  | 2.0                 | 1.8                  | 2.1                 | 1.7                  | 2.0                 | 1.8                  | 2.1                    | 2.3                  |
| Edema/swelling                                 | 1.0                 | 3.0                  | 1.3                 | 1.8                  | 0.9                 | 1.8                  | 0.4                    | 0.8                  |
| Fever                                          | 6.6                 | 5.4                  | 6.3                 | 6.4                  | 2.9                 | 2.4                  | 2.4                    | 2.1                  |
| Pain                                           | 1.1                 | 1.4                  | 1.4                 | 1.3                  | 0.6                 | 1.2                  | 0.2                    | 0.0                  |
| Pain, abdominal                                | 5.0                 | 5.8                  | 4.0                 | 5.9                  | 2.6                 | 3.6                  | 1.8                    | 2.7                  |
| Pain, chest                                    | 8.0                 | 9.0                  | 8.4                 | 10.8                 | 1.8                 | 3.2                  | 1.7                    | 3.3                  |
| Pain, pelvic                                   | 5.6                 | 6.5                  | 4.5                 | 5.5                  | 0.6                 | 1.1                  | 0.3                    | 0.0                  |
| Reaction, vasovagal                            | 1.4                 | 3.5                  | 1.2                 | 0.7                  | 0.4                 | 0.9                  | 0.3                    | 0.2                  |
| <b>Cardiovascular System</b>                   | <b>56.8</b>         | <b>65.6</b>          | <b>50.6</b>         | <b>58.7</b>          | <b>26.2</b>         | <b>36.9</b>          | <b>22.3</b>            | <b>24.4</b>          |
| Angina, unstable                               | 1.3                 | 1.6                  | 0.9                 | 1.7                  | 3.4                 | 3.6                  | 3.1                    | 4.1                  |
| Bleeding, postoperative                        | 32.9                | 35.7                 | 24.1                | 26.4                 | 5.0                 | 10.5                 | 1.8                    | 2.5                  |
| Bradycardia                                    | 3.5                 | 4.2                  | 3.1                 | 2.0                  | 0.7                 | 1.5                  | 1.7                    | 0.8                  |
| Dissection, coronary artery                    | 4.4                 | 4.7                  | 4.5                 | 4.0                  | 0.2                 | 0.2                  | 0.3                    | 0.0                  |
| Heart failure                                  | 1.4                 | 2.5                  | 1.7                 | 2.2                  | 1.5                 | 2.7                  | 2.7                    | 2.9                  |
| Hematoma                                       | 9.5                 | 13.0                 | 5.6                 | 9.2                  | 2.5                 | 4.4                  | 0.8                    | 3.3                  |
| Hemorrhage                                     | 0.8                 | 2.3                  | 1.6                 | 3.1                  | 0.4                 | 0.8                  | 0.3                    | 0.0                  |
| Hemorrhage, I.V. site                          | 4.4                 | 7.7                  | 3.0                 | 6.8                  | 2.1                 | 4.8                  | 0.7                    | 2.3                  |
| Hypotension                                    | 6.6                 | 10.2                 | 7.9                 | 8.6                  | 2.9                 | 5.1                  | 2.6                    | 1.8                  |
| Infused vein complication                      | 1.2                 | 4.0                  | 1.8                 | 3.1                  | 1.8                 | 3.3                  | 1.0                    | 0.8                  |
| Phlebitis/thrombophlebitis                     | 0.4                 | 0.9                  | 0.5                 | 1.1                  | 0.7                 | 2.1                  | 0.8                    | 1.2                  |
| Premature ventricular contraction              | 1.7                 | 1.6                  | 2.2                 | 1.8                  | 0.8                 | 0.9                  | 0.7                    | 0.4                  |
| Ventricular tachycardia                        | 2.1                 | 1.2                  | 3.3                 | 2.6                  | 1.1                 | 1.4                  | 0.5                    | 0.8                  |
| <b>Digestive System</b>                        | <b>24.2</b>         | <b>33.6</b>          | <b>22.1</b>         | <b>31.2</b>          | <b>12.6</b>         | <b>20.8</b>          | <b>9.8</b>             | <b>12.9</b>          |
| Acid regurgitation                             | 1.2                 | 1.6                  | 0.7                 | 2.9                  | 0.3                 | 1.1                  | 0.3                    | 0.4                  |
| Constipation                                   | 5.0                 | 6.0                  | 4.6                 | 5.7                  | 3.7                 | 5.3                  | 2.4                    | 2.1                  |
| Diarrhea                                       | 0.9                 | 2.6                  | 1.3                 | 2.4                  | 0.7                 | 1.5                  | 0.6                    | 1.6                  |
| Dyspepsia                                      | 2.2                 | 1.6                  | 2.2                 | 2.0                  | 1.3                 | 1.2                  | 1.2                    | 1.6                  |
| Nausea                                         | 9.5                 | 16.5                 | 10.9                | 16.9                 | 2.9                 | 8.6                  | 3.7                    | 5.8                  |
| Vomiting                                       | 4.0                 | 8.8                  | 4.5                 | 7.3                  | 1.1                 | 4.1                  | 1.4                    | 1.8                  |
| <b>Endocrine System</b>                        | <b>0.1</b>          | <b>0.9</b>           | <b>0.0</b>          | <b>0.0</b>           | <b>0.3</b>          | <b>0.0</b>           | <b>0.2</b>             | <b>0.0</b>           |
| <b>Hemic and Lymphatic System</b>              | <b>0.6</b>          | <b>2.8</b>           | <b>0.4</b>          | <b>1.5</b>           | <b>1.0</b>          | <b>1.5</b>           | <b>0.4</b>             | <b>0.2</b>           |
| <b>Metabolic/Nutritional/Immune</b>            | <b>1.3</b>          | <b>11</b>            | <b>1.0</b>          | <b>3.1</b>           | <b>1.0</b>          | <b>0.8</b>           | <b>0.8</b>             | <b>0.0</b>           |
| <b>Musculoskeletal System</b>                  | <b>26.9</b>         | <b>32.0</b>          | <b>27.6</b>         | <b>31.0</b>          | <b>5.8</b>          | <b>9.8</b>           | <b>3.7</b>             | <b>6.8</b>           |
| Pain, arm                                      | 1.4                 | 2.6                  | 1.1                 | 2.4                  | 0.1                 | 0.8                  | 0.3                    | 0.0                  |
| Pain, back                                     | 21.8                | 24.8                 | 22.5                | 22.6                 | 2.3                 | 5.4                  | 1.8                    | 2.7                  |
| Pain, leg                                      | 2.0                 | 4.0                  | 1.3                 | 2.6                  | 0.4                 | 0.8                  | 0.0                    | 1.6                  |
| Pain, shoulder                                 | 1.1                 | 1.9                  | 1.6                 | 2.4                  | 0.8                 | 0.9                  | 0.3                    | 1.2                  |

18.0 Appendix Six: Clinical Adverse Event tables (cont)

Table 18.0.5 Adverse events in the phase II-III tirofiban database according to sex of subject (cont)<sup>a</sup>.

|                                | Tirofiban + Heparin |          | Heparin/ Procedures |          | Tirofiban |          | Heparin/ No Procedures |          |
|--------------------------------|---------------------|----------|---------------------|----------|-----------|----------|------------------------|----------|
|                                | N=1384              | N=569    | N=1342              | N=545    | N=1368    | N=664    | N=1146                 | N=513    |
|                                | Male %              | Female % | Male %              | Female % | Male %    | Female % | Male %                 | Female % |
| Nervous System and Psychiatric | 31.5                | 36.2     | 34.1                | 34.5     | 22.9      | 30.0     | 20.6                   | 22.8     |
| Agitation                      | 1.6                 | 1.4      | 2.0                 | 0.9      | 0.4       | 1.1      | 0.3                    | 0.2      |
| Anxiety                        | 7.0                 | 5.3      | 7.6                 | 8.4      | 4.0       | 3.5      | 3.0                    | 2.7      |
| Anxiety disorder               | 0.9                 | 2.3      | 1.1                 | 1.1      | 0.7       | 1.7      | 0.2                    | 0.0      |
| Confusion                      | 2.0                 | 1.6      | 1.8                 | 2.4      | 0.7       | 1.2      | 0.7                    | 1.2      |
| Dizziness                      | 2.2                 | 3.9      | 1.9                 | 2.8      | 1.2       | 3.8      | 0.9                    | 1.0      |
| Headache                       | 16.5                | 19.0     | 18.6                | 21.5     | 14.8      | 18.1     | 13.5                   | 16.0     |
| Insomnia                       | 6.7                 | 6.5      | 7.0                 | 6.4      | 4.2       | 5.6      | 3.4                    | 4.5      |
| Nervousness                    | 2.0                 | 2.5      | 1.8                 | 1.5      | 0.1       | 0.9      | 0.3                    | 0.4      |
| Somnolence                     | 0.9                 | 1.6      | 1.3                 | 2.2      | 0.4       | 1.4      | 0.1                    | 0.2      |
| Respiratory System             | 14.7                | 18.8     | 12.1                | 15.4     | 12.1      | 17.2     | 7.8                    | 10.9     |
| Cough                          | 1.4                 | 2.3      | 1.8                 | 1.3      | 0.7       | 1.2      | 0.6                    | 0.2      |
| Dyspnea                        | 2.3                 | 2.5      | 2.2                 | 3.5      | 1.1       | 1.7      | 1.3                    | 0.6      |
| Edema, pulmonary               | 0.7                 | 1.2      | 1.0                 | 0.9      | 1.1       | 1.7      | 1.0                    | 2.3      |
| Epistaxis                      | 4.8                 | 7.6      | 0.6                 | 2.2      | 5.3       | 8.7      | 0.4                    | 2.5      |
| Rales/rhonchi                  | 2.5                 | 2.1      | 2.4                 | 4.0      | 1.2       | 2.1      | 1.3                    | 1.6      |
| Skin and Skin Appendage        | 17.3                | 16.7     | 12.7                | 15.0     | 5.3       | 8.0      | 2.3                    | 4.7      |
| Ecchymosis                     | 10.8                | 12.0     | 7.2                 | 10.5     | 1.5       | 3.0      | 0.1                    | 0.8      |
| Sweating                       | 2.0                 | 1.1      | 1.4                 | 0.9      | 0.7       | 0.5      | 0.1                    | 0.2      |
| Special Senses                 | 1.4                 | 0.7      | 1.2                 | 1.7      | 0.8       | 1.2      | 0.4                    | 0.6      |
| Urogenital System              | 7.7                 | 12.5     | 6.4                 | 13.2     | 3.8       | 6.5      | 3.2                    | 5.5      |
| Hematuria                      | 3.5                 | 3.2      | 1.9                 | 3.1      | 1.5       | 0.8      | 1.1                    | 0.8      |
| Infection, urinary tract       | 0.9                 | 4.6      | 4.6                 | 4.0      | 0.4       | 2.9      | 0.5                    | 2.7      |

a. Data from NDA volume 1.37, table D-76.

D. Overall Adverse Events grouped according to age of the subjects (~65,265 years of age)

Table 18.0.6 below shows the percentage of subjects with clinical adverse experiences under the age of 65 years compared to subjects 65 years and older, occurring in 22.0% of subjects in any of the age subgroups/treatment group categories.

Table 18.0.6 Adverse events in the phase II-III database separated by age of subject<sup>a</sup>.

| Adverse Events                                            | Tirofiban + Heparin |             | Heparin/ Procedures |             | Tirofiban    |             | Heparin/ No Procedures |             |
|-----------------------------------------------------------|---------------------|-------------|---------------------|-------------|--------------|-------------|------------------------|-------------|
|                                                           | N=1174 <65 %        | N=779 ≥65 % | N=1122 <65 %        | N=765 ≥65 % | N=1093 <65 % | N=939 ≥65 % | N=920 <65 %            | N=739 ≥65 % |
| Percent of subjects with clinical adverse experience (AE) | 84.7                | 89.0        | 81.8                | 84.2        | 56.3         | 62.4        | 46.8                   | 57.5        |
| Percent of subjects without clinical AE                   | 15.3                | 11.0        | 18.2                | 15.8        | 43.7         | 37.6        | 53.2                   | 42.5        |
| Body as a Whole/Site Unspecified                          | 32.9                | 34.3        | 30.5                | 33.5        | 16.3         | 19.7        | 11.6                   | 18.1        |
| Asthenia/fatigue                                          | 2.3                 | 2.7         | 2.0                 | 3.8         | 1.6          | 1.4         | 0.5                    | 0.3         |
| Death                                                     | 0.3                 | 4.5         | 1.0                 | 4.7         | 1.3          | 5.0         | 2.0                    | 6.0         |
| Drug overdose                                             | 2.0                 | 1.9         | 2.0                 | 1.8         | 2.1          | 1.8         | 1.7                    | 2.7         |
| Edema/swelling                                            | 1.3                 | 2.1         | 1.2                 | 1.8         | 1.5          | 0.9         | 0.4                    | 0.7         |
| Fever                                                     | 6.0                 | 6.7         | 6.0                 | 6.9         | 3.0          | 2.4         | 2.2                    | 2.4         |
| Pain, abdominal                                           | 5.1                 | 5.4         | 3.8                 | 5.6         | 3.0          | 2.9         | 1.7                    | 2.6         |
| Pain, chest                                               | 9.6                 | 6.3         | 9.8                 | 8.1         | 2.5          | 2.0         | 2.5                    | 1.8         |
| Pain, pelvic                                              | 6.6                 | 4.7         | 5.6                 | 3.5         | 0.7          | 0.7         | 0.4                    | 0.0         |
| Reaction, vasovagal                                       | 2.0                 | 2.1         | 1.4                 | 0.5         | 0.7          | 0.4         | 0.2                    | 0.3         |

18.0 Appendix Six: Clinical Adverse Event tables (cant)

Table 18.0.6 Adverse events in the phase II-III database separated by age of subject (cont)<sup>a</sup>.

| Adverse Events<br>+ Heparin                 | Tirofiban          |                   | Heparin/<br>Procedures |                   | Tirofiban          |                   | Heparin/<br>No Procedures |                   |
|---------------------------------------------|--------------------|-------------------|------------------------|-------------------|--------------------|-------------------|---------------------------|-------------------|
|                                             | N=1174<br><65<br>% | N=779<br>≥65<br>% | N=1122<br><65<br>%     | N=765<br>≥65<br>% | N=1093<br><65<br>% | N=939<br>≥65<br>% | N=920<br><65<br>%         | N=739<br>≥65<br>% |
| <b>Cardiovascular System</b>                |                    | 62.4              | 49.2                   | 58.4              | 24.8               | 35.5              | 17.3                      | 30.0              |
| Angina, unstable                            | 1.2                | 1.7               | 0.8                    | 1.6               | 3.2                | 3.8               | 2.6                       | 4.5               |
| Bleeding, postoperative                     | 31.8               | 36.7              | 24.3                   | 25.5              | 5.4                | 8.5               | 2.0                       | 2.2               |
| Bradycardia                                 | 3.7                | 3.7               | 2.6                    | 3.0               | 0.9                | 1.1               | 1.1                       | 1.8               |
| Dissection, coronary artery                 | 5.5                | 3.1               | 4.3                    | 4.6               | 0.2                | 0.2               | 0.2                       | 0.1               |
| Heart failure                               | 0.9                | 2.8               | 1.0                    | 3.1               | 1.1                | 2.8               | 1.4                       | 4.5               |
| Hematoma                                    | 9.8                | 1.7               | 16.0                   | 7.6               | 1.8                | 4.6               | 0.5                       | 2.8               |
| Hemorrhage                                  | 0.9                | 1.7               | 1.9                    | 2.4               | 0.5                | 0.6               | 0.1                       | 0.3               |
| Hemorrhage, I.V. site                       | 3.7                | 7.8               | 2.0                    | 7.1               | 1.9                | 4.3               | 1.0                       | 1.5               |
| Hypotension                                 | 8.0                | 7.2               | 7.3                    | 9.3               | 3.0                | 4.4               | 1.7                       | 3.1               |
| Infused vein complication                   | 1.8                | 2.4               | 2.2                    | 2.1               | 2.4                | 2.1               | 0.9                       | 1.1               |
| Premature ventricular contraction           | 1.6                | 1.7               | 1.7                    | 2.7               | 1.1                | 0.5               | 0.7                       | 0.5               |
| Shock, cardiogenic                          | 0.5                | 1.8               | 0.4                    | 1.4               | 0.7                | 2.1               | 0.7                       | 1.6               |
| Ventricular tachycardia                     | 2.0                | 1.5               | 2.9                    | 3.3               | 1.0                | 1.4               | 0.8                       | 0.4               |
| <b>Digestive System</b>                     | 24.4               | 30.7              | 22.9                   | 27.3              | 13.6               | 17.1              | 10.4                      | 11.1              |
| Constipation                                | 5.0                | 5.6               | 4.2                    | 6.0               | 3.0                | 5.5               | 2.2                       | 2.6               |
| Diarrhea                                    | 1.0                | 2.1               | 0.8                    | 2.9               | 1.0                | 1.0               | 0.7                       | 1.2               |
| Dyspepsia                                   | 1.8                | 2.4               | 2.4                    | 1.8               | 1.6                | 1.0               | 1.4                       | 1.2               |
| Nausea                                      | 10.7               | 12.8              | 12.2                   | 13.2              | 4.8                | 4.6               | 3.9                       | 4.9               |
| Vomiting                                    | 4.0                | 7.6               | 4.7                    | 6.3               | 2.1                | 2.0               | 1.3                       | 1.8               |
| <b>Endocrine System</b>                     | 0.1                | 0.6               | 0.0                    | 0.0               | 0.0                | 0.4               | 0.1                       | 0.1               |
| <b>Hemic and Lymphatic System</b>           | 0.8                | 1.9               | 0.5                    | 0.9               | 0.8                | 1.5               | 0.3                       | 0.4               |
| <b>Metabolic/Nutritional/Immune Systems</b> | 1.1                | 1.4               | 1.3                    | 2.1               | 0.8                | 1.1               | 0.5                       | 0.5               |
| <b>Musculoskeletal System</b>               | 28.9               | 27.6              | 30.6                   | 25.8              | 7.0                | 7.2               | 4.7                       | 4.6               |
| Pain, back                                  | 23.7               | 21.2              | 24.8                   | 19.2              | 3.4                | 3.3               | 2.3                       | 1.9               |
| Pain, leg                                   | 2.5                | 2.7               | 2.0                    | 1.3               | 0.3                | 0.9               | 0.2                       | 0.8               |
| <b>Nervous System and Psychiatric</b>       | 32.5               | 33.4              | 34.8                   | 33.2              | 27.1               | 23.0              | 22.2                      | 20.2              |
| Agitation                                   | 0.9                | 2.6               | 1.1                    | 2.6               | 0.1                | 1.2               | 0.1                       | 0.5               |
| Anxiety                                     | 6.0                | 7.3               | 7.5                    | 8.4               | 4.5                | 3.1               | 2.7                       | 3.1               |
| Confusion                                   | 0.6                | 3.9               | 0.9                    | 3.5               | 0.0                | 1.8               | 0.2                       | 1.6               |
| Dizziness                                   | 2.6                | 2.8               | 2.0                    | 2.4               | 1.9                | 2.1               | 0.9                       | 0.9               |
| Headache                                    | 19.6               | 13.6              | 21.7                   | 16.1              | 19.1               | 12.1              | 16.2                      | 11.9              |
| Insomnia                                    | 6.7                | 6.5               | 7.0                    | 6.5               | 5.3                | 3.9               | 4.1                       | 3.2               |
| Nervousness                                 | 1.5                | 3.0               | 1.4                    | 2.1               | 0.2                | 0.6               | 0.2                       | 0.4               |
| Somnolence                                  | 0.7                | 1.7               | 0.9                    | 2.5               | 0.5                | 1.1               | 0.0                       | 0.3               |
| <b>Respiratory System</b>                   | 12.5               | 20.9              | 10.8                   | 16.5              | 11.3               | 16.6              | 7.0                       | 11.0              |
| Cough                                       | 1.0                | 2.7               | 1.7                    | 1.6               | 0.6                | 1.1               | 0.3                       | 0.7               |
| Dyspnea                                     | 1.6                | 3.5               | 2.0                    | 3.5               | 1.3                | 1.3               | 1.0                       | 1.2               |
| Edema, pulmonary                            | 0.6                | 1.2               | 0.3                    | 2.0               | 0.4                | 2.3               | 0.9                       | 2.2               |
| Epistaxis                                   | 4.1                | 7.8               | 1.0                    | 1.2               | 5.5                | 7.5               | 1.1                       | 1.1               |
| Rales/rhonchi                               | 1.7                | 3.3               | 2.0                    | 4.1               | 1.5                | 1.6               | 1.6                       | 1.1               |
| <b>Skin and Skin Appendage</b>              | 14.5               | 21.1              | 13.3                   | 13.6              | 5.4                | 7.1               | 2.1                       | 4.2               |
| Ecchymosis                                  | 9.9                | 13.0              | 7.6                    | 8.9               | 1.2                | 2.9               | 0.0                       | 0.7               |
| Sweating                                    | 1.5                | 2.1               | 1.7                    | 0.7               | 0.6                | 0.5               | 0.0                       | 0.3               |
| <b>Special Senses</b>                       | 1.2                | 1.2               | 1.2                    | 1.4               | 0.7                | 1.2               | 0.0                       | 1.1               |
| <b>Urogenital</b>                           | 6.7                | 10.8              | 3.4                    | 6.2               | 6.8                | 12.5              | 3.0                       | 5.0               |
| Hematuria                                   | 1.7                | 3.0               | 0.8                    | 1.8               | 2.7                | 4.5               | 1.0                       | 1.1               |
| Infection, urinary tract                    | 1.3                | 2.5               | 0.8                    | 1.6               | 1.6                | 2.4               | 1.1                       | 1.4               |

a. Data from NDA volume 1.37, table D-72.

18.0 Appendix Six: Clinical Adverse Event tables (cont)

E. Occurrence of AEs in the phase II-III database, grouped according to presence or absence of hypertension

The table below shows the percentage of subjects with clinical adverse experiences grouped according to the presence or absence of hypertension at time of study entry, occurring in 22.0% of subjects in any of the age subgroups/treatment group categories.

Table 18.0.7 Adverse events in the phase II-III database separated by presence or absence of hypertension (HTN)<sup>ab</sup>.

|                                             | Tirofiban + Heparin |         | Heparin/ Procedures |         | Tirofiban |         | Heparin/ No Procedures |         |
|---------------------------------------------|---------------------|---------|---------------------|---------|-----------|---------|------------------------|---------|
|                                             | HTN                 | Non-HTN | HTN                 | Non-HTN | HTN       | Non-HTN | HTN                    | Non-HTN |
|                                             | N=1068              | N=885   | N=1059              | N=828   | N=1082    | N=950   | N=906                  | N=753   |
| <b>Percent of patients with clinical AE</b> | 87.6                | 84.9    | 83.3                | 82.1    | 59.8      | 58.3    | 52.0                   | 51.1    |
| <b>Body as a Whole</b>                      | 34.5                | 32.2    | 32.0                | 31.3    | 18.2      | 17.5    | 14.7                   | 14.3    |
| Asthenia/fatigue                            | 1.9                 | 3.2     | 2.5                 | 3.1     | 1.0       | 2.1     | 0.6                    | 0.3     |
| Death                                       | 2.2                 | 1.7     | 2.9                 | 1.9     | 3.2       | 2.7     | 3.0                    | 4.6     |
| Drug overdose                               | 2.4                 | 1.4     | 2.0                 | 1.9     | 1.7       | 2.3     | 2.9                    | 1.3     |
| Fever                                       | 6.6                 | 5.9     | 6.6                 | 6.0     | 3.1       | 2.3     | 2.5                    | 2.0     |
| Pain                                        | 1.1                 | 1.2     | 1.5                 | 1.2     | 0.7       | 0.8     | 0.2                    | 0.0     |
| Pain, abdominal                             | 4.5                 | 6.1     | 4.7                 | 4.3     | 3.2       | 2.6     | 2.0                    | 2.3     |
| Pain, chest                                 | 8.6                 | 7.9     | 10.0                | 8.0     | 2.4       | 2.1     | 2.4                    | 1.9     |
| Pain, pelvic                                | 6.0                 | 5.8     | 3.9                 | 5.9     | 0.6       | 0.9     | 0.3                    | 0.1     |
| Reaction, vasovagal                         | 2.2                 | 1.9     | 1.0                 | 1.1     | 0.6       | 0.6     | 0.2                    | 0.3     |
| <b>Cardiovascular System</b>                | 59.9                | 58.6    | 55.0                | 50.4    | 29.9      | 29.6    | 22.0                   | 24.2    |
| Angina, unstable                            | 1.6                 | 1.1     | 1.5                 | 0.6     | 3.8       | 3.2     | 3.1                    | 3.9     |
| Bleeding, postoperative                     | 34.4                | 33.0    | 25.7                | 23.7    | 7.1       | 6.5     | 2.2                    | 1.9     |
| Bradycardia                                 | 3.5                 | 4.1     | 2.9                 | 2.5     | 0.6       | 1.4     | 1.3                    | 1.5     |
| Dissection, coronary artery                 | 4.3                 | 4.7     | 4.2                 | 4.7     | 0.3       | 0.1     | 0.1                    | 0.3     |
| Heart failure                               | 2.0                 | 1.4     | 1.8                 | 1.9     | 2.1       | 1.6     | 2.0                    | 3.7     |
| Hematoma                                    | 10.7                | 10.4    | 7.1                 | 6.0     | 3.2       | 2.9     | 1.9                    | 1.2     |
| Hemorrhage                                  | 1.6                 | 0.8     | 2.7                 | 1.2     | 0.6       | 0.5     | 0.1                    | 0.3     |
| Hemorrhage, I.V. site                       | 5.3                 | 5.4     | 4.2                 | 4.0     | 3.1       | 2.8     | 1.4                    | 0.9     |
| Hypotension                                 | 6.3                 | 9.4     | 6.7                 | 9.9     | 3.3       | 4.0     | 2.3                    | 2.4     |
| Infused vein complication                   | 2.3                 | 1.7     | 1.7                 | 2.8     | 2.0       | 2.5     | 0.4                    | 1.6     |
| Premature ventricular contraction           | 1.2                 | 2.1     | 1.8                 | 2.5     | 1.0       | 0.6     | 0.6                    | 0.7     |
| Ventricular tachycardia                     | 1.6                 | 2.1     | 2.8                 | 3.4     | 1.0       | 1.4     | 0.8                    | 0.4     |
| <b>Digestive System</b>                     | 27.1                | 26.8    | 25.6                | 23.6    | 15.1      | 15.5    | 11.9                   | 9.3     |
| Constipation                                | 5.1                 | 5.5     | 4.5                 | 5.4     | 3.7       | 4.7     | 2.2                    | 2.5     |
| Pain, shoulder                              | 1.4                 | 1.2     | 2.2                 | 1.3     | 0.7       | 0.9     | 0.3                    | 0.8     |
| Diarrhea                                    | 1.0                 | 1.9     | 2.5                 | 0.6     | 1.0       | 0.9     | 1.1                    | 0.7     |
| Dyspepsia                                   | 1.8                 | 2.4     | 1.9                 | 2.5     | 1.6       | 0.9     | 1.3                    | 1.3     |
| Nausea                                      | 12.5                | 10.5    | 13.0                | 12.1    | 4.9       | 4.5     | 5.5                    | 2.9     |
| Vomiting                                    | 5.3                 | 5.5     | 5.9                 | 4.6     | 1.8       | 2.4     | 1.8                    | 1.2     |
| <b>Endocrine System</b>                     | 0.5                 | 0.1     | 0.0                 | 0.0     | 0.1       | 0.3     | 0.2                    | 0.0     |
| Hemic and Lymphatic System                  | 1.6                 | 0.8     | 1.0                 | 0.2     | 1.0       | 1.3     | 0.2                    | 0.5     |
| Metabolic/Nutritional/Immune                | 1.4                 | 1.0     | 1.8                 | 1.4     | 0.9       | 0.9     | 0.8                    | 0.3     |
| <b>Musculoskeletal System</b>               | 28.2                | 28.6    | 28.3                | 29.0    | 7.3       | 6.9     | 5.2                    | 4.0     |
| Pain, arm                                   | 2.1                 | 1.5     | 1.7                 | 1.2     | 0.4       | 0.3     | 0.2                    | 0.3     |
| Pain, back                                  | 22.3                | 23.2    | 21.5                | 23.8    | 3.7       | 2.9     | 2.3                    | 1.9     |
| Pain, leg                                   | 2.6                 | 2.5     | 1.3                 | 2.2     | 0.6       | 0.4     | 0.8                    | 0.1     |

18.0 Appendix Six: Clinical Adverse Event tables (cont)

Table 18.0.7 Adverse events in the phase II-III database separated by presence or absence of hypertension (HTN)<sup>a,b</sup>.

|                                       | Tirofiban + Heparin |                  | Heparin/ Procedures |                  | Tirofiban     |                  | Heparin/ No Procedures |                  |
|---------------------------------------|---------------------|------------------|---------------------|------------------|---------------|------------------|------------------------|------------------|
|                                       | HTN<br>N=1068       | Non-HTN<br>N=885 | HTN<br>N=1059       | Non-HTN<br>N=828 | HTN<br>N=1082 | Non-HTN<br>N=950 | HTN<br>N=906           | Non-HTN<br>N=753 |
| <b>Nervous System and Psychiatric</b> | 31.7                | 34.2             | 33.0                | 35.7             | 25.3          | 25.1             | 23.0                   | 19.3             |
| Agitation                             | 1.7                 | 1.4              | 2.0                 | 1.3              | 0.5           | 0.7              | 0.3                    | 0.3              |
| Anxiety                               | 6.6                 | 6.3              | 8.4                 | 7.1              | 3.8           | 3.9              | 3.3                    | 2.4              |
| Confusion                             | 2.0                 | 1.8              | 2.6                 | 1.1              | 0.6           | 1.1              | 0.8                    | 0.9              |
| Dizziness                             | 2.5                 | 2.8              | 2.1                 | 2.3              | 2.4           | 1.6              | 0.9                    | 0.9              |
| Headache                              | 15.8                | 18.9             | 18.7                | 20.4             | 15.1          | 16.8             | 16.0                   | 12.2             |
| Insomnia                              | 6.7                 | 6.6              | 7.2                 | 6.4              | 5.2           | 4.1              | 4.0                    | 3.5              |
| Nervousness                           | 2.2                 | 2.0              | 2.1                 | 1.2              | 0.5           | 0.3              | 0.4                    | 0.1              |
| <b>Respiratory System</b>             | 17.9                | 13.4             | 14.0                | 12.0             | 15.0          | 12.4             | 9.5                    | 7.8              |
| Cough                                 | 2.2                 | 1.1              | 1.7                 | 1.6              | 1.0           | 0.6              | 0.6                    | 0.4              |
| Dyspnea                               | 2.5                 | 2.1              | 2.4                 | 2.9              | 1.4           | 1.2              | 1.3                    | 0.8              |
| E p i s t a x i s                     | 6.8                 | 4.1              | 1.2                 | 0.8              | 7.1           | 5.6              | 0.8                    | 1.5              |
| Rales/rhonchi                         | 2.8                 | 1.8              | 3.0                 | 2.7              | 1.4           | 1.7              | 1.8                    | 0.9              |
| <b>Skin and Skin Appendage</b>        | 16.9                | 17.4             | 14.1                | 12.6             | 5.9           | 6.5              | 3.5                    | 2.4              |
| Ecchymosis                            | 11.1                | 11.1             | 8.6                 | 7.5              | 1.8           | 2.1              | 0.4                    | 0.1              |
| Sweating                              | 1.5                 | 2.0              | 1.1                 | 1.4              | 0.5           | 0.7              | 0.1                    | 0.1              |
| <b>Special Senses</b>                 | 1.0                 | 1.4              | 1.3                 | 1.3              | 0.6           | 1.3              | 0.6                    | 0.4              |
| <b>Urogenital System</b>              | 10.9                | 6.9              | 8.6                 | 8.1              | 5.8           | 3.4              | 4.0                    | 3.9              |
| Hematuria                             | 4.3                 | 2.4              | 2.5                 | 1.8              | 1.9           | 0.5              | 0.9                    | 1.2              |
| Infection, urinary tract              | 2.4                 | 1.4              | 2.0                 | 1.6              | 1.8           | 0.4              | 1.7                    | 0.7              |

a. Data from NDA volume 1.37, table 105.

b. This table contains percentages of patients counted. Patients with more than one clinical adverse experience in a body system are counted only once in that body system total and in the overall total. Any individual clinical adverse experience that reached the 2.0% incidence level in any subgroup/treatment group category was included in this table. If no individual adverse experiences reached the 2.0% level, then just the body system is shown, provided at least 1 patient in any treatment group had an adverse experience in that body system.

18.0 Appendix Six: Clinical Adverse Event tables (cont)

F. Occurrence of AEs in the phase II-III database, grouped according to presence or absence of hypercholesterolemia

The table below shows the percentage of subjects with clinical adverse experiences grouped according to the presence or absence of hypercholesterolemia at time of study entry, occurring in 22.0% of subjects in any of the age subgroups/treatment group categories.

Table 18.0.8 Adverse events in the phase II-III database separated by presence or absence of hypercholesterolemia<sup>a,b</sup>

|                                      | Tirofiban + Heparin    |                      | Heparin/ Procedures    |                      | Tirofiba n             |                       | Heparin/ No Procedures |                      |
|--------------------------------------|------------------------|----------------------|------------------------|----------------------|------------------------|-----------------------|------------------------|----------------------|
|                                      | Elevated Chol<br>n=983 | Normal Chol<br>n=970 | Elevated Chol<br>n=932 | Normal Chol<br>n=955 | Elevated Chol<br>n=955 | Normal Chol<br>n=1077 | Elevated Chol<br>n=778 | Normal Chol<br>n=881 |
| Percent of patients with clinical AE | 88.2                   | 84.5                 | 84.1                   | 81.5                 | 59.9                   | 58.3                  | 53.6                   | 49.8                 |
| Body as a Whole                      | 35.1                   | 31.5                 | 33.5                   | 9.9                  | 19.3                   | 16.5                  | 15.2                   | 13.8                 |
| Asthenia/fatigue                     | 2.7                    | 2.2                  | 3.6                    | 1.9                  | 2.2                    | 0.9                   | 0.8                    | 0.1                  |
| Death                                | 1.8                    | 2.2                  | 2.5                    | 2.5                  | 2.7                    | 3.2                   | 2.7                    | 4.7                  |
| Drug overdose                        | 1.9                    | 1.8                  | 2.1                    | 1.8                  | 1.8                    | 2.0                   | 2.4                    | 1.8                  |
| Fever                                | 6.8                    | 5.8                  | 6.2                    | 6.5                  | 3.4                    | 2.2                   | 2.3                    | 2.3                  |
| Pain, abdominal                      | 5.3                    | 5.2                  | 5.3                    | 3.9                  | 2.7                    | 3.2                   | 2.6                    | 1.7                  |
| Pain, chest                          | 9.0                    | 7.6                  | 9.4                    | 8.8                  | 2.2                    | 2.3                   | 2.6                    | 1.8                  |
| Pain, pelvic                         | 6.9                    | 4.8                  | 5.9                    | 3.7                  | 1.4                    | 0.2                   | 0                      | 0.2                  |
| Reaction, vasovagal                  | 2.7                    | 1.3                  | 1.5                    | 0.6                  | 0.8                    | 0.4                   | 0.3                    | 0.2                  |
| Cardiovascular System                | 62.4                   | 56.3                 | 54.7                   | 51.2                 | 31.1                   | 28.5                  | 22.2                   | 23.7                 |
| Angina, unstable                     | 1.5                    | 1.2                  | 0.6                    | 1.6                  | 3.4                    | 3.6                   | 3.5                    | 3.5                  |
| Bleeding, postoperative              | 35.7                   | 31.8                 | 26.4                   | 23.2                 | 7.1                    | 6.6                   | 2.7                    | 1.5                  |
| Bradycardia                          | 3.3                    | 4.2                  | 2.0                    | 3.5                  | 1.0                    | 0.9                   | 1.4                    | 1.4                  |
| Dissection, coronary artery          | 4.8                    | 4.2                  | 4.4                    | 4.4                  | 0.3                    | 0.1                   | 0.3                    | 0.1                  |
| Heart Failure                        | 1.7                    | 1.6                  | 1.7                    | 2.0                  | 2.3                    | 1.5                   | 1.7                    | 3.7                  |
| Hematoma                             | 10.3                   | 10.8                 | 7.5                    | 5.8                  | 3.8                    | 2.5                   | 2.2                    | 1.0                  |
| Hemorrhage                           | 1.6                    | 0.8                  | 2.1                    | 2.0                  | 0.5                    | 0.6                   | 0.3                    | 0.1                  |
| Hemorrhage, I.V. site                | 5.6                    | 5.2                  | 5.4                    | 2.8                  | 3.8                    | 2.3                   | 1.4                    | 1.0                  |
| Hypotension                          | 7.3                    | 8.0                  | 7.4                    | 8.8                  | 3.7                    | 3.6                   | 2.1                    | 2.6                  |
| Infused vein complication            | 2.2                    | 1.9                  | 3.3                    | 1.0                  | 2.4                    | 2.1                   | 0.8                    | 1.1                  |
| Premature ventricular contraction    | 1.5                    | 1.8                  | 1.8                    | 2.4                  | 0.7                    | 0.9                   | 0.8                    | 0.5                  |
| Ventricular tachycardia              | 2.0                    | 1.6                  | 2.6                    | 3.6                  | 0.7                    | 1.6                   | 0.5                    | 0.7                  |
| Digestive System                     | 26.6                   | 27.3                 | 26.2                   | 23.2                 | 15.9                   | 14.7                  | 11.2                   | 10.3                 |
| Constipation                         | 5.5                    | 5.1                  | 5.4                    | 4.5                  | 3.8                    | 4.5                   | 3.1                    | 1.7                  |
| Dyspepsia                            | 1.8                    | 2.3                  | 2.3                    | 2.1                  | 1.7                    | 0.9                   | 1.3                    | 1.4                  |
| Nausea                               | 12.2                   | 10.9                 | 14.2                   | 11.1                 | 4.6                    | 4.8                   | 5.0                    | 3.7                  |
| Vomiting                             | 4.5                    | 6.4                  | 5.9                    | 4.8                  | 2.2                    | 1.9                   | 1.9                    | 1.1                  |
| Endocrine System                     | 0.2                    | 0.4                  | 0.0                    | 0.0                  | 0.2                    | 0.2                   | 0.1                    | 0.1                  |
| Hemic and Lymphatic System           | 1.3                    | 1.1                  | 0.9                    | 0.5                  | 0.9                    | 1.3                   | 0.1                    | 0.6                  |
| Metabolic/Nutritional/Immune         | 0.9                    | 1.5                  | 1.7                    | 1.6                  | 1.0                    | 0.8                   | 0.9                    | 0.2                  |
| Musculoskeletal System               | 31.0                   | 25.7                 | 29.4                   | 27.9                 | 8.2                    | 6.2                   | 5.8                    | 3.6                  |
| Pain, back                           | 25.1                   | 20.2                 | 22.7                   | 22.3                 | 3.9                    | 2.9                   | 2.6                    | 1.7                  |
| Pain, leg                            | 2.2                    | 2.9                  | 1.8                    | 1.6                  | 0.4                    | 0.6                   | 0.1                    | 0.8                  |
| Pain, shoulder                       | 1.1                    | 1.5                  | 2.1                    | 1.5                  | 0.8                    | 0.8                   | 0.9                    | 0.2                  |
| Nervous System and Psychiatric       | 33.3                   | 32.5                 | 34.3                   | 34.0                 | 26.5                   | 24.0                  | 22.0                   | 20.7                 |
| Anxiety                              | 6.9                    | 6.1                  | 8.5                    | 7.2                  | 4.8                    | 3.0                   | 3.1                    | 2.7                  |
| Confusion                            | 1.2                    | 2.6                  | 1.8                    | 2.1                  | 0.4                    | 1.2                   | 0.5                    | 1.1                  |
| Dizziness                            | 3.1                    | 2.3                  | 2.0                    | 2.3                  | 2.1                    | 1.9                   | 0.8                    | 1.0                  |
| Headache                             | 17.4                   | 17.0                 | 20.3                   | 18.6                 | 16.2                   | 15.6                  | 14.3                   | 14.3                 |
| Insomnia                             | 7.3                    | 6.0                  | 7.5                    | 6.2                  | 5.5                    | 3.9                   | 5.1                    | 2.5                  |
| Nervousness                          | 1.7                    | 2.5                  | 2.1                    | 1.3                  | 0.2                    | 0.6                   | 0.5                    | 0.1                  |
| Somnolence                           | 1.2                    | 0.9                  | 2.3                    | 0.8                  | 1.2                    | 0.4                   | 0.3                    | 0.0                  |

18.0 Appendix Six: Clinical Adverse Event tables (cont)

Table 18.0.8 Adverse events in the phase II-III database separated by presence or absence of hypercholesterolemia (cont)<sup>a,b</sup>.

|                          | Tirofiban + Heparin    |                      | Heparin/ Procedures    |                      | Tirofiban              |                       | Heparin/ No Procedures |                      |
|--------------------------|------------------------|----------------------|------------------------|----------------------|------------------------|-----------------------|------------------------|----------------------|
|                          | Elevated Chol<br>n=983 | Normal Chol<br>n=970 | Elevated Chol<br>n=932 | Normal Chol<br>n=955 | Elevated Chol<br>n=955 | Normal Chol<br>n=1077 | Elevated Chol<br>n=778 | Normal Chol<br>n=881 |
| Respiratory System       | 15.5                   | 16.3                 | 13.0                   | 13.2                 | 14.8                   | 12.9                  | 9.1                    | 8.4                  |
| Cough                    | 1.2                    | 2.2                  | 1.6                    | 1.7                  | 1.2                    | 0.6                   | 0.5                    | 0.5                  |
| Dyspnea                  | 2.5                    | 2.2                  | 2.5                    | 2.7                  | 1.4                    | 1.2                   | 1.5                    | 0.7                  |
| Epistaxis                | 6.1                    | 5.1                  | 1.1                    | 1.0                  | 7.3                    | 5.6                   | 0.9                    | 1.2                  |
| Rales/rhonchi            | 2.1                    | 2.6                  | 2.6                    | 3.1                  | 1.5                    | 1.6                   | 1.7                    | 1.1                  |
| Skin and Skin Appendage  | 17.1                   | 17.1                 | 14.3                   | 12.6                 | 6.9                    | 5.6                   | 2.8                    | 3.2                  |
| Ecchymosis               | 11.6                   | 10.6                 | 8.6                    | 7.6                  | 2.2                    | 1.8                   | 0.1                    | 0.5                  |
| Special Senses           | 1.8                    | 0.5                  | 0.9                    | 1.8                  | 0.7                    | 1.1                   | 0.5                    | 0.5                  |
| Urogenital System        | 9.1                    | 9.1                  | 9.0                    | 7.7                  | 4.6                    | 4.7                   | 4.0                    | 3.9                  |
| Hematuria                | 3.3                    | 3.6                  | 2.7                    | 1.8                  | 1.2                    | 1.4                   | 0.8                    | 1.2                  |
| Infection, urinary tract | 1.9                    | 2.0                  | 1.8                    | 1.8                  | 0.9                    | 1.4                   | 1.4                    | 1.0                  |

a. Data from NDA volume 1.37, table D-113.

b. This table contains percentages of patients counted. Patients with more than one clinical adverse experience in a body system are counted only once in that body system total and in the overall total. Any individual clinical adverse experience that reached the 2.0% incidence level in any subgroup/treatment group category was included in this table. If no individual adverse experiences reached the 2.0% level, then just the body system is shown, provided at least 1 patient in any treatment group had an adverse experience in that body system.

G. Occurrence of AEs in the phase II-III database, grouped according to presence or absence of diabetes

The table below shows the percentage of subjects with clinical adverse experiences grouped according to the presence or absence of diabetes at time of study entry, occurring in 22.0% of subjects in any of the age subgroups/treatment group categories.

Table 18.0.9 Adverse events in the phase II-III database separated by presence or absence of diabetes<sup>a,b</sup>.

|                                      | Tirofiban +Heparin |                        | Heparin/ Prcedures |                        | Tirofiban         |                        | Heparin/ No Procedures |                        |
|--------------------------------------|--------------------|------------------------|--------------------|------------------------|-------------------|------------------------|------------------------|------------------------|
|                                      | Diabetic<br>N=405  | Non-diabetic<br>N=1548 | Diabetic<br>N=408  | Non-diabetic<br>N=1479 | Diabetic<br>N=421 | Non-diabetic<br>N=1611 | Diabetic<br>N=373      | Non-diabetic<br>N=1286 |
| Percent of patients with clinical AE | 87.4               | 86.1                   | 83.6               | 82.6                   | 63.9              | 57.8                   | 52.3                   | 51.4                   |
| Body as a Whole                      | 36.5               | 32.5                   | 34.1               | 31.0                   | 16.6              | 16.9                   | 13.8                   |                        |
| Asthenia/fatigue                     | 2.2                | 2.5                    | 3.2                | 2.6                    | 1.4               | 1.6                    | 0.5                    | 0.4                    |
| Death                                | 2.7                | 1.8                    | 3.9                | 2.1                    | 3.1               | 3.0                    | 4.3                    | 3.6                    |
| Drug overdose                        | 1.5                | 1.9                    | 1.7                | 2.0                    | 2.1               | 1.9                    | 2.9                    | 1.9                    |
| Edema/swelling                       | 2.7                | 1.3                    | 2.7                | 1.1                    | 1.7               | 1.1                    | 0.3                    | 0.6                    |
| Fever                                | 4.2                | 6.8                    | 6.6                | 6.3                    | 4.3               | 2.4                    | 4.0                    | 1.8                    |
| Pain                                 | 2.0                | 1.0                    | 1.2                | 1.4                    | 0.7               | 0.8                    | 0.0                    | 0.2                    |
| Pain, abdominal                      | 6.2                | 5.0                    | 4.4                | 4.6                    | 3.8               | 2.7                    | 1.9                    | 2.2                    |
| Pain, chest                          | 9.9                | 7.9                    | 8.8                | 9.2                    | 3.1               | 2.0                    | 2.4                    | 2.1                    |
| Pain, pelvic                         | 6.4                | 5.7                    | 4.2                | 4.9                    | 0.5               | 0.8                    | 0.0                    | 0.3                    |
| Reaction, vasovagal                  | 1.5                | 2.2                    | 0.7                | 1.1                    | 0.7               | 0.6                    | 0.0                    | 0.3                    |

18.0 Appendix six: Clinical Adverse Event tables (cont)

Table 18.0.9 Adverse events in the phase II-III database separated by presence or absence of diabetes (cont)<sup>a,b</sup>

|                                   | Tirofiban +Heparin |                     | Heparin/Procedur |                     | Tirofibaο      |                     | Heparin/No Proctires |                     |
|-----------------------------------|--------------------|---------------------|------------------|---------------------|----------------|---------------------|----------------------|---------------------|
|                                   | Diabetic N=405     | Non-diabetic N=1548 | Diabetic N=408   | Non-diabetic N=1479 | Diabetic N=421 | Non-diabetic N=1611 | Diabetic N=373       | Non-diabetic N=1286 |
| Angina, unstable                  | 1.0                | 1.5                 | 1.7              | 0.9                 | 4.0            | 3.4                 | 2.7                  | 3.7                 |
| Bleeding, postoperative           | 30.4               | 34.6                | 22.5             | 25.4                | 6.7            | 6.9                 | 1.6                  | 2.2                 |
| Bradycardia                       | 3.0                | 3.9                 | 2.0              | 3.0                 | 0.0            | 1.2                 | 2.1                  | 1.2                 |
| Dissection, coronary artery       | 3.2                | 4.8                 | 2.7              | 4.9                 | 0.5            | 0.1                 | 0.3                  | 0.2                 |
| Heart failure                     | 2.7                | 1.4                 | 2.7              | 1.6                 | 3.3            | 1.5                 | 4.0                  | 2.4                 |
| Hematoma                          | 8.4                | 11.1                | 6.6              | 6.6                 | 3.1            | 3.1                 | 1.1                  | 1.7                 |
| Hemorrhage                        | 1.2                | 1.2                 | 1.7              | 2.2                 | 0.2            | 0.6                 | 0.0                  | 0.2                 |
| Hemorrhage, I.V. site             | 5.2                | 5.4                 | 5.6              | 3.7                 | 4.5            | 2.6                 | 1.9                  | 1.0                 |
| Hypotension                       | 6.7                | 7.9                 | 8.1              | 8.1                 | 4.3            | 3.5                 | 2.9                  | 2.2                 |
| Infused vein complication         | 3.0                | 1.8                 | 2.0              | 2.2                 | 1.7            | 2.4                 | 0.5                  | 1.1                 |
| Premature ventricular contractioi | 1.7                | 1.6                 | 1.5              | 2.3                 | 1.2            | 0.7                 | 1.1                  | 0.5                 |
| Shock, cardiogenic                | 1.2                | 1.0                 | 0.5              | 0.9                 | 2.1            | 1.1                 | 1.3                  | 0.9                 |
| Ventricular tachycardia           | 1.5                | 1.9                 | 2.5              | 3.2                 | 0.5            | 1.4                 | 0.5                  | 0.6                 |
| Digestive System                  | 25.4               | 27.3                | 24.3             | 24.8                | 16.4           | 15.0                | 10.7                 | 10.7                |
| Acid regurgitation                | 1.7                | 1.2                 | 2.0              | 1.2                 | 1.2            | 0.4                 | 0.3                  | 1.4                 |
| Constipation                      | 5.2                | 5.3                 | 4.9              | 4.9                 | 3.8            | 4.3                 | 1.6                  | 2.6                 |
| Dyspepsia                         | 1.5                | 2.2                 | 1.2              | 2.4                 | 0.7            | 1.4                 | 1.1                  | 1.4                 |
| Nausea                            | 11.1               | 11.7                | 12.7             | 12.6                | 5.5            | 4.5                 | 4.8                  | 4.2                 |
| Vomiting                          | 5.7                | 5.4                 | 5.9              | 5.2                 | 2.6            | 1.9                 | 0.8                  | 1.7                 |
| Endocrine System                  | 0.7                | 0.2                 | 0.0              | 0.0                 | 0.5            | 0.1                 | 0.3                  | 0.1                 |
| Hemic and Lymphatic System        | 2.5                | 0.9                 | 1.0              | 0.6                 | 1.9            | 0.9                 | 0.5                  | 0.3                 |
| Metabolic/Nutritional/Immune      | 2.0                | 1.0                 | 3.2              | 1.2                 | 1.4            | 0.8                 | 0.3                  | 0.6                 |
| Musculoskeletal System            | 25.2               | 29.2                | 28.2             | 28.7                | 8.8            | 6.7                 | 5.4                  | 4.4                 |
| Pain, arm                         | 2.2                | 1.7                 | 2.2              | 1.3                 | 0.7            | 0.2                 | 0.3                  | 0.2                 |
| Pain, back                        | 20.5               | 23.3                | 20.6             | 23.1                | 3.8            | 3.2                 | 2.4                  | 2.0                 |
| Pain, leg                         | 2.2                | 2.6                 | 2.2              | 1.6                 | 1.4            | 0.3                 | 0.5                  | 0.5                 |
| Pain, shoulder                    | 1.2                | 1.4                 | 2.2              | 1.7                 | 0.5            | 0.9                 | 0.8                  | 0.5                 |
| Nervous System and Psychiatric    | 32.1               | 33.1                | 31.9             | 34.8                | 25.2           | 25.2                | 22.0                 | 21.1                |
| Agitation                         | 1.7                | 1.5                 | 2.0              | 1.6                 | 0.7            | 0.6                 | 0.5                  | 0.2                 |
| Anxiety                           | 6.9                | 6.4                 | 8.1              | 7.8                 | 3.6            | 3.9                 | 2.1                  | 3.1                 |
| Confusion                         | 1.7                | 1.9                 | 3.7              | 1.5                 | 1.2            | 0.7                 | 1.3                  | 0.7                 |
| Dizziness                         | 3.2                | 2.5                 | 2.9              | 2.0                 | 1.4            | 2.2                 | 1.9                  | 0.6                 |
| Headache                          | 16.0               | 17.5                | 17.4             | 20.0                | 15.9           | 15.9                | 13.7                 | 14.5                |
| Insomnia                          | 5.2                | 7.0                 | 6.9              | 6.8                 | 5.5            | 4.5                 | 3.2                  | 3.9                 |
| Nervousness                       | 4.0                | 1.6                 | 1.2              | 1.8                 | 0.5            | 0.4                 | 0.5                  | 0.2                 |
| Somnolence                        | 1.5                | 1.0                 | 2.7              | 1.2                 | 1.2            | 0.6                 | 0.3                  | 0.1                 |
| Respiratory System                | 20.2               | 14.7                | 14.7             | 12.6                | 18.5           | 12.5                | 11.8                 | 7.9                 |
| Cough                             | 2.5                | 1.5                 | 1.0              | 1.8                 | 1.7            | 0.6                 | 0.3                  | 0.5                 |
| Dyspnea                           | 3.0                | 2.2                 | 2.5              | 2.6                 | 1.7            | 1.2                 | 1.3                  | 1.0                 |
| Edema, pulmonary                  | 1.2                | 0.7                 | 1.2              | 0.9                 | 2.1            | 1.1                 | 2.9                  | 1.0                 |
| Epistaxis                         | 7.4                | 5.1                 | 1.0              | 1.1                 | 10.0           | 5.5                 | 0.8                  | 1.2                 |
| Rales/rhonchi                     | 1.7                | 2.5                 | 3.2              | 2.8                 | 2.1            | 1.4                 | 1.3                  | 1.4                 |
| Skin and Skin Appendage           | 14.6               | 7.8                 | 11.3             | 14.0                | 7.6            | 5.8                 | 4.3                  | 2.6                 |
| Ecchymosis                        | 7.9                | 12.0                | 7.4              | 8.3                 | 2.4            | 1.9                 | 0.5                  | 0.2                 |
| Sweating                          | 2.5                | 1.6                 | 1.2              | 1.3                 | 0.7            | 0.6                 | 0.0                  | 0.2                 |
| Special Senses                    | 0.5                | 1.4                 | 2.0              | 1.1                 | 1.0            | 0.9                 | 0.5                  | 0.5                 |
| Urogenital System                 | 13.1               | 8.0                 | 12.3             | 7.3                 | 5.9            | 4.3                 | 5.1                  | 3.6                 |
| Hematuria                         | 4.9                | 3.0                 | 3.2              | 2.0                 | 2.1            | 1.1                 | 1.1                  | 1.0                 |
| Infection, urinary tract          | 3.5                | 1.6                 | 2.5              | 1.6                 | 1.2            | 1.2                 | 2.1                  | 0.9                 |

a. Data from NDA volume 1.37, table D-1109.

b. This table contains percentages of patients counted. Patients with more than one clinical adverse experience in a body system are counted only once in that body system total and in the overall total. Shown are clinical adverse experience that reached the 2.0% incidence level.

18.0 Appendix Six: Clinical Adverse Event tables (cont)

H. Occurrence of AEs in the phase II-III database, for those subjects who received ticlopidine during their respective trials

The table below shows the percentage of subjects who received ticlopidine with clinical adverse experiences grouped according study drug received.

Table 18.0.10 Percentage (%) of subjects receiving ticlopidine with clinical AEs in the phase II-III database<sup>a,b</sup>

| Anticoagulant/antiplatelet drug                | Tirofiban + Heparin<br>n=1953 | Heparin/<br>Procedures<br>n=1887 | Tirofiban<br>n=2032 | Heparin/<br>No<br>Procedures<br>n=1659 |
|------------------------------------------------|-------------------------------|----------------------------------|---------------------|----------------------------------------|
| <b>Percent of subjects with clinical AE</b>    | 84.3                          | 79.9                             | 62.5                | 50.0                                   |
| <b>Percent of subjects without clinical AE</b> | 15.7                          | 20.1                             | 37.5                | 50.0                                   |
| <b>Body as a Whole</b>                         | 34.0                          | 26.9                             | 21.4                | 11.8                                   |
| Asthenia/fatigue                               | 0.0                           | 0.0                              | 5.4                 | 0.0                                    |
| Fever                                          | 3.3                           | 4.5                              | 3.6                 | 5.9                                    |
| Pain, abdominal                                | 7.8                           | 3.0                              | 0.0                 | 0.0                                    |
| Pain, chest                                    | 13.7                          | 11.9                             | 7.1                 | 0.0                                    |
| <b>Cardiovascular System</b>                   | 64.0                          | 61.2                             | 25.0                | 11.8                                   |
| Bleeding, postoperative                        | 27.5                          | 31.3                             | 8.9                 | 5.9                                    |
| Dissection, coronary artery                    | 27.5                          | 21.6                             | 0.0                 | 0.0                                    |
| Hematoma                                       | 11.1                          | 5.2                              | 3.6                 | 0.0                                    |
| Hypotension                                    | 3.9                           | 9.7                              | 3.6                 | 0.0                                    |
| Ventricular tachycardia                        | 1.3                           | 3.7                              | 1.8                 | 5.9                                    |
| <b>Digestive System</b>                        | 28.8                          | 26.9                             | 21.4                | 14.7                                   |
| Constipation                                   | 5.2                           | 4.5                              | 3.6                 | 5.9                                    |
| Nausea                                         | 10.5                          | 17.2                             | 7.1                 | 5.9                                    |
| Vomiting                                       | 7.2                           | 8.2                              | 3.6                 | 0.0                                    |
| <b>Hemic and Lymphatic System</b>              | 0.0                           | 0.7                              | 0.0                 | 0.0                                    |
| Metabolic/Nutritional/Immune                   | 0.7                           | 0.7                              | 1.8                 | 0.0                                    |
| <b>Musculoskeletal System</b>                  | 28.1                          | 35.8                             | 17.9                | 8.8                                    |
| Pain, back                                     | 21.6                          | 29.9                             | 8.9                 | 2.9                                    |
| <b>Nervous System and Psychiatric</b>          | 26.8                          | 26.1                             | 30.4                | 23.5                                   |
| Anxiety                                        | 4.6                           | 6.7                              | 3.6                 | 5.9                                    |
| Headache                                       | 14.4                          | 15.7                             | 25.0                | 11.8                                   |
| Insomnia                                       | 5.9                           | 5.2                              | 7.1                 | 5.9                                    |
| <b>Respiratory System</b>                      | 11.8                          | 8.2                              | 7.1                 | 2.9                                    |
| <b>Skin and Skin Appendage</b>                 | 19.0                          | 6.7                              | 3.6                 | 0.0                                    |
| Ecchymosis                                     | 13.7                          | 4.5                              | 0.0                 | 0.0                                    |
| <b>Special Senses</b>                          | 1.3                           | 0.7                              | 0.0                 | 0.0                                    |
| <b>Urogenital System</b>                       | 10.5                          | 9.0                              | 5.4                 | 2.9                                    |

<sup>a</sup> Data from NDA volume 1.37, table D-87, shown as percent of subjects with available data

<sup>b</sup> This table contains percentages of subjects counted. Patients with more than one clinical adverse experience in a body system are counted only once in that body system total and in the overall total. Any individual clinical adverse experience that reached the 5.0% incidence level in any treatment group category was included in this table. If no individual adverse experiences reached the 5.0% level, then just the body system is shown, provided at least 1 patient in any treatment group had an adverse experience in that body system.

18.0 Appendix Six: Clinical Adverse Event tables (cont)

I. Occurrence of AEs in the phase II-III database, for those subjects who received warfarin during their respective trials

The table below shows the percentage of subjects who received warfarin with clinical adverse experiences grouped according study drug received.

Table 18.0.11 Percentage of subjects receiving warfarin with clinical AEs in the phase II-III database<sup>a,b</sup>

| Anticoagulant/antiplatelet drug       | Tirofiban + Heparin<br>n=196 | Heparin/ Procedures<br>n=207 | Tirofiban<br>n=32 | Heparin/ No Procedures<br>n=38 |
|---------------------------------------|------------------------------|------------------------------|-------------------|--------------------------------|
| Percent of subjects with clinical AE  | 92.3                         | 85.5                         | 71.9              | 73.7                           |
| Body as a Whole                       | 41.8                         | 37.7                         | 18.8              | 18.4                           |
| Death                                 | 1.0                          | 0.0                          | 3.1               | 5.3                            |
| Drug overdose                         | 1.0                          | 0.5                          | 0.0               | 5.3                            |
| Fever                                 | 7.1                          | 9.7                          | 0.0               | 2.6                            |
| Pain, abdominal                       | 8.2                          | 4.3                          | 0.0               | 2.6                            |
| Pain, chest                           | 17.9                         | 15.0                         | 3.1               | 0.0                            |
| Pain, pelvic                          | 10.2                         | 6.8                          | 6.3               | 2.6                            |
| <b>Cardiovascular System</b>          | 74.5                         | 64.3                         | 40.6              | 42.1                           |
| Angina, unstable                      | 1.0                          | 0.0                          | 0.0               | 5.3                            |
| Bleeding, postoperative               | 42.9                         | 30.9                         | 9.4               | 2.6                            |
| Bradycardia                           | 5.1                          | 3.9                          | 6.3               | 5.3                            |
| Dissection, coronary artery           | 23.0                         | 23.7                         | 0.0               | 5.3                            |
| Heart failure                         | 2.6                          | 2.4                          | 0.0               | 10.5                           |
| Hematoma                              | 16.3                         | 5.8                          | 6.3               | 2.6                            |
| Hypotension                           | 7.1                          | 7.7                          | 9.4               | 0.0                            |
| Ventricular tachycardia               | 3.1                          | 5.8                          | 0.0               | 0.0                            |
| <b>Digestive System</b>               | 31.1                         | 27.5                         | 25.0              | 5.3                            |
| Constipation                          | 4.1                          | 3.4                          | 3.1               | 5.3                            |
| Nausea                                | 15.8                         | 16.9                         | 12.5              | 0.0                            |
| Vomiting                              | 7.1                          | 6.8                          | 3.1               | 0.0                            |
| <b>Hemic and Lymphatic System</b>     | 1.0                          | 1.0                          | 0.0               | 2.6                            |
| <b>Metabolic/Nutritional/Immune</b>   | 1.5                          | 2.4                          | 3.1               | 0.0                            |
| <b>Musculoskeletal System</b>         | 37.8                         | 37.2                         | 9.4               | 7.9                            |
| Pain, back                            | 34.7                         | 31.4                         | 6.3               | 7.9                            |
| <b>Nervous System and Psychiatric</b> | 27.6                         | 26.6                         | 37.5              | 31.6                           |
| Anxiety                               | 3.1                          | 6.3                          | 12.5              | 2.6                            |
| Dizziness                             | 1.5                          | 1.0                          | 3.1               | 7.9                            |
| Headache                              | 12.8                         | 14.5                         | 21.9              | 23.7                           |
| Insomnia                              | 5.6                          | 4.8                          | 3.1               | 0.0                            |
| Malaise                               | 2.6                          | 0.5                          | 6.3               | 0.0                            |
| <b>Respiratory System</b>             | 14.8                         | 14.0                         | 18.8              | 13.2                           |
| Epistaxis                             | 3.6                          | 0.0                          | 6.3               | 0.0                            |
| Rales/rhonchi                         | 5.1                          | 2.4                          | 3.1               | 2.6                            |
| <b>Skin and Skin Appendage</b>        | 25.5                         | 14.0                         | 15.6              | 5.3                            |
| Ecchymosis                            | 18.9                         | 11.1                         | 0.0               | 0.0                            |
| Pruritus                              | 3.1                          | 0.0                          | 3.1               | 5.3                            |
| Sweating                              | 1.0                          | 1.9                          | 6.3               | 0.0                            |
| <b>Special Senses</b>                 | 1.5                          | 1.9                          | 0.0               | 0.0                            |
| <b>Urogenital System</b>              | 9.7                          | 9.7                          | 6.3               | 5.3                            |

a. Data from NDA volume 1.37, table D-89.

b. This table contains percentages of subjects counted. Patients with more than one clinical adverse experience in a body system are counted only once in that body system total and in the overall total. Any individual clinical adverse experience that reached the 5.0% incidence level in any treatment group category was included in this table. If no individual adverse experiences reached the 5.0% level, then just the body system is shown, provided at least 1 patient in any treatment group had an adverse experience in that body system.

18.0 Appendix Six: Clinical Adverse Event tables (cont)

**J. Occurrence of AEs in the phase II-III database, for those subjects who received B-blockers during their respective trials**

The table below shows the percentage of subjects who received h-blockers with clinical adverse experiences grouped according study drug received.

Table 18.0.12 Percentage of subjects receiving D-block ; with clinical AEs in the phase II-III database<sup>a,b</sup>

|                                      | Tirofiban<br>+ Heparin<br>n=1490 | Heparin/<br>Procedures<br>n=1462 | Tirofiban<br>n=1450 | Heparin/<br>No<br>Procedures<br>n=1192 |
|--------------------------------------|----------------------------------|----------------------------------|---------------------|----------------------------------------|
| Percent of subjects with clinical AE | 86.4                             | 83.1                             | 59.6                | 51.1                                   |
| <b>Body as a Whole</b>               | <b>33.0</b>                      | <b>31.8</b>                      | <b>17.8</b>         | <b>14.9</b>                            |
| Fever                                | 6.7                              | 6.4                              | 2.8                 | 2.7                                    |
| Pain, chest                          | 8.2                              | 9.1                              | 1.7                 | 2.3                                    |
| Pain, pelvic                         | 5.8                              | 4.8                              | 0.8                 | 0.3                                    |
| <b>Cardiovascular System</b>         | <b>60.4</b>                      | <b>53.6</b>                      | <b>31.7</b>         | <b>23.0</b>                            |
| Bleeding, postoperative              | 34.6                             | 25.4                             | 7.1                 | 2.3                                    |
| Hematoma                             | 10.4                             | 6.6                              | 3.5                 | 2.0                                    |
| Hypotension                          | 7.7                              | 8.7                              | 3.8                 | 2.6                                    |
| Digestive System                     | 27.2                             | 25.0                             | 14.6                | 10.2                                   |
| Constipation                         | 5.1                              | 5.0                              | 3.4                 | 1.7                                    |
| Nausea                               | 11.7                             | 12.7                             | 4.1                 | 4.5                                    |
| Vomiting                             | 5.7                              | 5.8                              | 2.1                 | 1.5                                    |
| Endocrine                            | 0.3                              | 0.0                              | 0.2                 | 0.1                                    |
| <b>Hemic/Lymphatic System</b>        | <b>1.3</b>                       | <b>0.8</b>                       | <b>1.2</b>          | <b>0.3</b>                             |
| Metabolic/Nutritional/Immune         | 1.2                              | 1.6                              | 0.9                 | 0.6                                    |
| Musculoskeletal System               | 27.5                             | 27.6                             | 6.9                 | 4.5                                    |
| Pain, back                           | 22.1                             | 21.4                             | 3.4                 | 2.0                                    |
| Nervous System and Psychiatric       | 32.8                             | 35.1                             | 25.4                | 21.1                                   |
| Anxiety                              | 6.7                              | 8.2                              | 3.9                 | 3.0                                    |
| Headache                             | 17.3                             | 20.5                             | 16.1                | 14.3                                   |
| Insomnia                             | 6.7                              | 7.3                              | 4.8                 | 3.2                                    |
| <b>Respiratory System</b>            | <b>15.8</b>                      | <b>13.3</b>                      | <b>13.0</b>         | <b>8.7</b>                             |
| Epistaxis                            | 5.3                              | 1.0                              | 5.9                 | 1.1                                    |
| <b>Skin and Skin Appendage</b>       | <b>17.5</b>                      | <b>13.4</b>                      | <b>6.3</b>          | <b>2.8</b>                             |
| Ecchymosis                           | 11.5                             | 7.7                              | 2.1                 | 0.3                                    |
| Special Senses                       | 1.3                              | 1.6                              | 0.9                 | 0.5                                    |
| Urogenital System                    | 9.3                              | 8.5                              | 4.8                 | 4.3                                    |

a. Data from NDA volume 1.37, table D-96.

b. This table contains percentages of subjects counted. Patients with more than one clinical adverse experience in a body system are counted only once in that body system total and in the overall total. Any individual clinical adverse experience that reached the 5.0% incidence level in any treatment group category was included in this table. If no individual adverse experiences reached the 5.0% level, then just the body system is shown, provided at least 1 patient in any treatment group had an adverse experience in that body system.

18.0 Appendix Six: Clinical Adverse Event tables (cont)

K. Occurrence of AEs in the phase II-III database, for those subjects who received calcium channel blockers during their respective trials

The table below shows the percentage of subjects who received calcium channel blockers, with clinical adverse experiences grouped according study drug received.

Table 18.0.13 Percentage of subjects receiving calcium channel blockers with clinical AEs in the phase II-III database<sup>a,b</sup>.

|                                             | Tirofiban<br>+ Heparin<br>n=1036 | Heparin/<br>Procedures<br>n=969 | Tirofiban<br>n=957 | Heparin/<br>No<br>Procedures<br>n=799 |
|---------------------------------------------|----------------------------------|---------------------------------|--------------------|---------------------------------------|
| <b>Percent of subjects with clinical AE</b> | 88.3                             | 84.5                            | 63.5               | 56.3                                  |
| <b>Body as a Whole</b>                      | 35.7                             | 34.8                            | 20.5               | 14.6                                  |
| Fever                                       | 7.2                              | 7.0                             | 2.6                | 2.5                                   |
| Pain chest                                  | 10.1                             | 10.3                            | 3.6                | 1.9                                   |
| Pain, pelvic                                | 6.0                              | 5.8                             | 0.6                | 0.4                                   |
| <b>Cardiovascular System</b>                | 62.4                             | 56.7                            | 33.4               | 26.4                                  |
| Bleeding, postoperative                     | 36.5                             | 28.2                            | 7.8                | 3.0                                   |
| Hematoma                                    | 11.4                             | 7.2                             | 4.2                | 1.6                                   |
| Hemorrhage, I.V. site                       | 5.7                              | 4.4                             | 3.8                | 1.6                                   |
| Hypotension                                 | 7.0                              | 8.0                             | 4.1                | 2.8                                   |
| <b>Digestive System</b>                     | 28.3                             | 26.5                            | 17.2               | 11.4                                  |
| Constipation                                | 5.1                              | 5.0                             | 4.9                | 2.8                                   |
| Nausea                                      | 12.7                             | 14.3                            | 5.6                | 4.8                                   |
| Vomiting                                    | 5.9                              | 5.5                             | 2.4                | 1.6                                   |
| <b>Endocrine</b>                            | 0.5                              | 0.0                             | 0.1                | 0.1                                   |
| <b>Hemic/Lymphatic</b>                      | 1.2                              | 1.1                             | 1.6                | 0.8                                   |
| <b>Metabolic/Nutritional/Immune</b>         | 1.3                              | 1.8                             | 1.3                | 0.9                                   |
| <b>Musculoskeletal System</b>               | 30.2                             | 33.6                            | 8.3                | 5.0                                   |
| Pain, back                                  | 24.2                             | 26.0                            | 3.9                | 2.6                                   |
| <b>Nervous System and Psychiatric</b>       | 31.8                             | 30.0                            | 26.5               | 23.5                                  |
| Anxiety                                     | 5.8                              | 7.1                             | 4.1                | 3.0                                   |
| Headache                                    | 15.1                             | 17.3                            | 15.5               | 16.0                                  |
| Insomnia                                    | 5.2                              | 6.2                             | 6.4                | 5.0                                   |
| <b>Respiratory System</b>                   | 17.0                             | 13.1                            | 16.9               | 9.5                                   |
| Epistaxis                                   | 6.5                              | 1.0                             | 8.5                | 1.0                                   |
| <b>Skin and Skin Appendage</b>              | 17.2                             | 14.0                            | 7.2                | 4.0                                   |
| Ecchymosis                                  | 11.6                             | 9.4                             | 2.2                | 0.4                                   |
| <b>Special Senses</b>                       | 1.3                              | 1.7                             | 1.0                | 0.4                                   |
| <b>Urogenital System</b>                    | 9.8                              | 9.7                             | 5.1                | 4.5                                   |

a. Data from NDA, volume 1, 37, table D-97.

b. This table contains percentages of subjects counted. Patients with more than one clinical adverse experience in a body system are counted only once in that body system total and in the overall total. Any individual clinical adverse experience that reached the 5.0% incidence level in any treatment group category was included in this table. If no individual adverse experiences reached the 5.0% level, then just the body system is shown, provided at least 1 patient in any treatment group had an adverse experience in that body system.

18.0 Appendix Six: Clinical Adverse Event tables (cont)

**L. Occurrence of AEs in the phase II-III database, for those subjects who received nitrates blockers during their respective trials**

The table below shows the percentage of subjects who received nitrates, with clinical adverse experiences grouped according study drug received.

Table 18.0.14 Percentage of subjects receiving nitrates with clinical AEs in the phase II-III database<sup>a,b</sup>.

|                                      | <b>Tirofiban<br/>+ Heparin<br/>n=1835</b> | <b>Heparin/<br/>Procedures<br/>n=1765</b> | <b>Tirofiban<br/>n=1799</b> | <b>Heparin/<br/>No Procedures<br/>n=1478</b> |
|--------------------------------------|-------------------------------------------|-------------------------------------------|-----------------------------|----------------------------------------------|
| Percent of subjects with clinical AE | 86.6                                      | 83.0                                      | 61.0                        | 52.9                                         |
| Body as a Whole                      | 34.2                                      | 32.5                                      | 18.8                        | 14.8                                         |
| Fever                                | 6.6                                       | 6.7                                       | 2.9                         | 2.4                                          |
| Pain, abdominal                      | 5.2                                       | 4.8                                       | 3.2                         | 2.1                                          |
| Pain, chest                          | 8.5                                       | 9.5                                       | 2.5                         | 2.2                                          |
| Pain, pelvic                         | 6.2                                       | 4.8                                       | 0.8                         | 0.3                                          |
| <b>Cardiovascular System</b>         | <b>59.6</b>                               | <b>53.0</b>                               | <b>30.7</b>                 | <b>23.7</b>                                  |
| Bleeding, postoperative              | 34.2                                      | 25.0                                      | 7.2                         | 2.2                                          |
| Hematoma                             | 10.7                                      | 6.5                                       | 3.4                         | 1.7                                          |
| Hemorrhage, I.V. site                | 5.3                                       | 4.0                                       | 3.0                         | 1.2                                          |
| Hypotension                          | 7.4                                       | 8.4                                       | 3.8                         | 2.4                                          |
| Digestive System                     | 26.9                                      | 25.5                                      | 16.2                        | 11.0                                         |
| Constipation                         | 5.2                                       | 5.0                                       | 4.2                         | 2.2                                          |
| Nausea                               | 11.7                                      | 13.1                                      | 5.2                         | 4.7                                          |
| Vomiting                             | 5.6                                       | 5.6                                       | 2.3                         | 1.6                                          |
| Endocrine                            | 0.3                                       | 0.0                                       | 0.2                         | 0.1                                          |
| <b>Hemic/Lymphatic</b>               | <b>1.3</b>                                | <b>0.7</b>                                | <b>1.2</b>                  | <b>0.4</b>                                   |
| Metabolic/Nutritional/Immune         | 1.3                                       | 1.7                                       | 0.9                         | 0.5                                          |
| Musculoskeletal System               | 28.2                                      | 28.6                                      | 7.4                         | 5.0                                          |
| Pain, back                           | 22.5                                      | 22.6                                      | 3.7                         | 2.4                                          |
| Nervous System and Psychiatric       | 33.6                                      | 34.8                                      | 27.1                        | 22.3                                         |
| Anxiety                              | 6.6                                       | 8.1                                       | 4.2                         | 3.0                                          |
| Headache                             | 18.0                                      | 20.3                                      | 17.3                        | 15.0                                         |
| Insomnia                             | 6.6                                       | 6.7                                       | 4.9                         | 4.1                                          |
| <b>Respiratory System</b>            | <b>16.1</b>                               | <b>13.7</b>                               | <b>14.3</b>                 | <b>9.3</b>                                   |
| Epistaxis                            | 5.6                                       | 1.1                                       | 6.7                         | 1.2                                          |
| <b>Skin and Skin Appendage</b>       | <b>16.9</b>                               | <b>13.1</b>                               | <b>6.5</b>                  | <b>3.1</b>                                   |
| Ecchymosis                           | 11.1                                      | 7.9                                       | 2.1                         | 0.3                                          |
| Special Senses                       | 1.3                                       | 1.4                                       | 0.9                         |                                              |
| Urogenital System                    | 9.3                                       | 8.7                                       | 4.9                         | 4.0                                          |

a. Data from NDA volume 1.37, table D-100.

b. This table contains percentages of subjects counted. Patients with more than one clinical adverse experience in a body system are counted only once in that body system total and in the overall total. Any individual clinical adverse experience that reached the 5.0% incidence level in any treatment group category was included in this table. If no individual adverse experiences reached the 5.0% level, then just the body system is shown, provided at least 1 patient in any treatment group had an adverse experience in that body system.

18.0 Appendix Six: Clinical Adverse Event tables (cont)

M. Occurrence of AEs in the phase II-III database, for those subjects who received non-steroidal anti-inflammatory drugs (NSAIDs) blockers during their respective trials

The table below shows the percentage of subjects who received NSAIDs with clinical adverse experiences grouped according study drug received.

Table 18.0.15 Percentage of subjects receiving NSAIDs with clinical AEs in the phase II-III database<sup>a,b</sup>

|                                      | Tirofiban + Heparin<br>n=188/1953<br>(9.6%) | Heparin/ Procedures<br>n=150/1887<br>(7.9%) | Tirofiban<br>n=85/2032<br>(4.2%) | Heparin/ No-Procedures<br>n=64/1659<br>(3.9%) |
|--------------------------------------|---------------------------------------------|---------------------------------------------|----------------------------------|-----------------------------------------------|
| Percent of subjects with clinical AE | 91.5                                        | 88.7                                        | 64.7                             | 70.3                                          |
| Body as a Whole                      | 41.5                                        | 32.7                                        | 17.6                             | 9.4                                           |
| Fever                                | 5.3                                         | 7.3                                         | 3.5                              | 0.0                                           |
| Pain, chest                          | 16.5                                        | 13.3                                        | 7.1                              | 1.6                                           |
| Pain, pelvic                         | 7.4                                         | 7.3                                         | 0.0                              | 0.0                                           |
| Cardiovascular System                | 62.2                                        | 55.3                                        | 31.8                             | 20.3                                          |
| Bleeding, postoperative              | 34.0                                        | 32.7                                        | 5.9                              | 0.0                                           |
| Dissection, coronary artery          | 6.4                                         | 5.3                                         | 0.0                              | 0.0                                           |
| Hematoma                             | 12.2                                        | 4.0                                         | 1.2                              | 1.6                                           |
| Hemorrhage                           | 1.6                                         | 5.3                                         | 0.0                              | 0.0                                           |
| Hypotension                          | 9.6                                         | 8.0                                         | 1.2                              | 0.0                                           |
| Digestive System                     | 30.9                                        | 20.0                                        | 21.2                             | 12.5                                          |
| Constipation                         | 5.9                                         | 6.0                                         | 3.5                              | 0.0                                           |
| Nausea                               | 15.4                                        | 10.7                                        | 10.6                             | 1.6                                           |
| Vomiting                             | 6.9                                         | 3.3                                         | 5.9                              | 1.6                                           |
| Hemic/Lymphatic                      | 0.0                                         | 2.0                                         | 1.2                              | 0.0                                           |
| Metabolic/Nutritional/Immune         | 0.5                                         | 2.0                                         | 2.4                              | 3.1                                           |
| Musculoskeletal System               | 38.8                                        | 38.0                                        | 14.1                             | 15.6                                          |
| Pain, back                           | 26.6                                        | 22.7                                        | 4.7                              | 0.0                                           |
| Nervous System and Psychiatric       | 37.2                                        | 28.0                                        | 29.4                             | 40.6                                          |
| Anxiety                              | 6.4                                         | 6.7                                         | 1.2                              | 3.1                                           |
| Headache                             | 20.2                                        | 17.3                                        | 23.5                             | 32.8                                          |
| Insomnia                             | 7.4                                         | 1.3                                         | 4.7                              | 3.1                                           |
| Nervousness                          | 5.9                                         | 3.3                                         | 0.0                              | 0.0                                           |
| Respiratory System                   | 18.1                                        | 8.0                                         | 11.8                             | 9.4                                           |
| Skin and Skin Appendage              | 18.6                                        | 10.7                                        | 4.7                              | 6.3                                           |
| Ecchymosis                           | 11.7                                        | 6.7                                         | 1.2                              | 0.0                                           |
| Urogenital System                    | 12.8                                        | 8.0                                         | 5.9                              | 4.7                                           |
| Special Senses                       | 0.5                                         | 2.0                                         | 2.4                              | 1.6                                           |
| Hematuria                            | 5.3                                         | 1.3                                         | 1.2                              | 1.6                                           |

a. Data from NDA volume 1.37, table D-103. Not all subjects had data for each test.

b. This table contains percentages of subjects counted. Patients with more than one clinical adverse experience in a body system are counted only once in that body system total and in the overall total. Any individual clinical adverse experience that reached the 5.0% incidence level in any treatment group category was included in this table. If no individual adverse experiences reached the 5.0% level, then just the body system is shown, provided at least 1 patient in any treatment group had an adverse experience in that body system.

## 19.0 Appendix Seven: Efficacy Summary for Reopro, Integrilin, and Plavix

Four drugs that work by inhibiting platelet aggregation via interaction with the IIb/IIIa platelet receptor have been submitted as NDAs: Reopro (abciximab); Plavix (clopidigrel); Integrilin (efibatide); and Aggrastat (tirofiban). Reopro and Plavix are approved for use. Integrilin and Aggrastat have been submitted as NDAs to the Division of Cardio-Renal Drug Products. Three of these drugs (Reopro, Integrilin, and Aggrastat) either have received or have proposed claims for the treatment of unstable angina/ non-Q-wave MI (UAP/NQWMI). These drugs are compared in the table below, followed by a discussion of the efficacy claims of the individual drugs.

### A. Reopro (Abciximab)

Reopro is approved as an adjunct therapy in two patient populations: 1) in patients undergoing PTCA, stent placement or atherectomy; and 2) in patients with unstable angina not responding to conventional medical therapy when percutaneous coronary intervention is planned within 24 hours.

Two trials support the use of Abciximab in subjects undergoing PTCA, stent placement or atherectomy: EPIC and EPILOGUE.

#### EPIC Trial

EPIC was a multicenter, double-blind, placebo-controlled trial of Abciximab in patients undergoing PTCA or atherectomy(1). A total of 2099 high-risk subjects undergoing PTCA were randomized to receive one of three therapies: 1) Abciximab bolus (0.25 mg/kg) followed by and Abcixir nab infusion (bolus plus infusion group) (10µg/minute); 2) Abcixir nab bolus (0.25 mg/kg) followed by a placebo infusion (bolus group); or 3) a placebo bolus followed by a placebo infusion (placebo group).

Patients were defined as high risk if they presented with: 1) acute evolving non-Q-wave MI (NQWMI), within 12 hours after the onset of symptoms that necessitated direct or rescue PTCA/atherectomy; 2) early postinfarction or unstable angina with at least two episodes of angina at rest associated with changes on resting ECG during the previous 24 hours, despite medical therapy; and 3) those at high risk for graft closure because of coronary morphology and/or clinical characteristics. Treatment with study agents was initiated 10-60 minutes before PTCA was begun. The table below shows the incidence of the combined primary endpoint and its components.

Table 19.0.1 Results at 30 day and 6 months from the EPIC trial<sup>a</sup>.

| Endpoint                              | Placebo<br>n=696 | Abciximab bolus<br>n=695                | Abciximab bolus + infusion<br>n=708     |
|---------------------------------------|------------------|-----------------------------------------|-----------------------------------------|
| <b>After 30 days</b>                  |                  |                                         |                                         |
| Death, MI or urgent revascularization | 89 (12.8%)       | 79 (11.5%)<br>p value vs. placebo 0.428 | 59 (8.3%)<br>p value vs. placebo 0.008  |
| Death                                 | 12 (1.7%)        | 9 (1.3%)                                | 12 (1.7%)                               |
| Acute MI in surviving patients        | 55 (7.9%)        | 40 (5.8%)                               | 31 (4.4%)                               |
| Urgent intervention                   | 22 (3.2%)        | 30 (4.4%)                               | 16 (2.2%)                               |
| <b>After 6 months</b>                 |                  |                                         |                                         |
| Death, MI or urgent revascularization | 122 (17.6%)      |                                         | 87 (12.3%)<br>p value vs. placebo 0.006 |

a. From Reopro package insert.

19.0 Appendix Seven: Efficacy Summary for Reopro, **Integrilin**, and Plavix

A. Reopro (Abciximab) (cont)

EPILOG Trial

EPILOG was a randomized, double-blind, placebo-controlled trial which evaluated Abciximab in a population undergoing percutaneous coronary intervention (excluding subjects with angina or NQWMI)(3). The trial tested the effect of a combination of Abciximab and two doses of heparin on the occurrence of cardiac events, compared with standard therapy (heparin + ASA).

The EPILOG trial primary endpoint was the occurrence of death (from any cause), myocardial infarction or reinfarction, or severe myocardial ischemia requiring **urgent** repeated coronary bypass surgery or repeated percutaneous coronary revascularization within 30 days of randomization.

A secondary endpoint of the EPILOG trial was the incidence of death, MI or CABG/PTCA (both urgent and non-urgent) within 6 months of randomization.

As shown in the table below, the use of Abciximab significantly lowered the incidence of the primary endpoint at the end of 30 days. The use of Abciximab also significantly lowered the incidence of death, MI or need for urgent revascularization before 30 days.

Table 19.0.2 Results at 30 days and 6 months from the EPILOG trial<sup>a</sup>.

| Endpoint                                                      | Placebo<br>+Standard-dose<br>Heparin<br><b>n=939</b> | Abciximab<br>+Standard-dose<br>Heparin<br><b>n=918</b> | Abciximab bolus<br>+Low-dose Heparin<br><b>n=935</b> |
|---------------------------------------------------------------|------------------------------------------------------|--------------------------------------------------------|------------------------------------------------------|
| <b>After 30 days</b>                                          |                                                      |                                                        |                                                      |
| Death or MI                                                   | 85 (9.1%)                                            | 38 (4.2%)<br><b>p value vs. placebo &lt;0.001</b>      | 35 (3.8%)<br><b>p value vs. placebo &lt;0.001</b>    |
| Death, MI or urgent revascularization                         | 109 (11.7%)                                          | 49 (5.4%)<br><b>p value vs. placebo &lt;0.001</b>      | 48 (5.2%)<br><b>p value vs. placebo &lt;0.001</b>    |
| Death                                                         | 7 (0.8%)                                             | 4 (0.4%)                                               | 3 (0.3%)                                             |
| <b>Acute</b> MI in surviving patients                         | 78 (8.4%)                                            | 34 (3.7%)                                              | 32 (3.4%)                                            |
| Urgent intervention                                           | 24 (2.6%)                                            | 11 (1.2%)                                              | 13 (1.4%)                                            |
| <b>After 6 months</b>                                         |                                                      |                                                        |                                                      |
| Death, MI or urgent revascularization                         | 138 (14.7%)                                          | 76 (8.3%)<br><b>p value vs. placebo &lt;0.001</b>      | 78 (8.4%)<br><b>p value vs. placebo &lt;0.001</b>    |
| Death, MI or repeat (urgent and non-urgent) revascularization | 241 (25.8%)                                          | 203 (22.3%)<br><b>p value vs. placebo =0.04</b>        | 212 (22.8%)<br><b>p value vs. placebo =0.07</b>      |

a. Data from Reopro package insert and (3).

## 19.0 Appendix Seven: Efficacy Summary for Reopro, Integrilin, and Plavix

### A. Reopro (Abciximab) (cont)

One trial was submitted to support the use of Abciximab in subjects with unstable angina not responding to conventional medical management when PTCA is planned within 24 hours: the CAPTURE trial(2).

#### CAPTURE Trial

CAPTURE was a randomized, double-blind, multicenter, placebo-controlled trial for Abciximab in unstable angina (2). The trial involved administering study drug 18 to 24 hours prior to the percutaneous coronary intervention (angioplasty, atherectomy, stent placement). The patients were eligible for enrollment in CAPTURE if they had **refractory** unstable angina, defined as myocardial ischemia persisting despite medical therapy including **heparin** and nitrates. Additionally, during screening angiogram eligible subjects were determined to have a lesion amenable to PTCA, which was to be performed within 24 hours of entry into the study. Randomized subjects then received a bolus Abciximab (25 **mg/kg IV**), followed by an infusion of **10µg/minute** versus placebo for 18-24 hours. At the end of the **infusion** period, the coronary intervention was performed. Subjects received **ASA** and **heparin** during this period as well. Overall, PTCA was performed **successfully** in 88.8% of the 635 placebo subjects and 94.0% of the 630 Abciximab subjects enrolled.

The table below shows the incidence of the primary endpoint. Note that there was a significant difference in the **primary** endpoint after 30 days, but not 6 months.

Table 19.0.3 Results at 30 days and 6 months from the CAPTURE trial<sup>a</sup>.

| Endpoint                                     | Placebo +Heparin<br>n=635 | Abciximab<br>+Heparin<br>n=630 | p value |
|----------------------------------------------|---------------------------|--------------------------------|---------|
| <i>After 30 days</i>                         |                           |                                |         |
| <b>Death, MI or urgent revascularization</b> | 101 (15.9%)               | 71 (11.3%)                     | 0.012   |
| Components of Primary Endpoint               |                           |                                |         |
| Death                                        | 8 (1.3%)                  | 6 (1.0%)                       |         |
| Acute MI in surviving patients               | 49 (7.7%)                 | 24 (3.8%)                      |         |
| Urgent intervention                          | 44 (6.9%)                 | 41 (6.6%)                      |         |
| <i>After 6 months</i>                        |                           |                                |         |
| <b>Death or MI</b>                           | 56 (9.0%)                 | 69 (10.9%)                     | 0.19    |
| <b>Death, MI or urgent revascularization</b> | 193 (30.8%)               | 193 (31.0%)                    | 0.77    |

a. Data from Reopro package insert.

### B. Plavix (Clopidogrel)

**Clopidogrel** is approved as **adjunct** therapy in subjects with atherosclerosis documented by recent stroke, recent myocardial infarction, or established peripheral vascular disease. Clopidogrel is not specifically approved for the treatment of **UAP/NQWMI**. The evidence of clinical efficacy is derived from the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial(9).

#### CAPRIE Trial

This was a randomized, double-blind, parallel-group study comparing clopidogrel to aspirin (**ASA**, 325 mg per day). The subjects randomized had at least one of the following: 1) recent MI (within 35 days); 2) recent ischemic stroke (within 6 months); or 3) objectively established peripheral vascular disease. Subjects received clopidogrel for an average of 1.6 years. The table below shows the incidence of new ischemic stroke (IS), new myocardial infarction, or other vascular death in the trial. Deaths not easily attributable to nonvascular causes were categorized as vascular.

Table 19.0.4 Results of the CAPRIE study<sup>a</sup>.

| Endpoint                               | ASA<br>n=9586 | Plavix<br>n=9599         |
|----------------------------------------|---------------|--------------------------|
| <b>IS, MI, or other vascular death</b> | 1019 (10.64%) | 939 (9.78%)              |
|                                        |               | p value versus ASA 0.045 |
| Components of Primary Endpoint         |               |                          |
| Ischemic stroke (IS)                   | 461 (4.81%)   | 438 (4.56%)              |
| MI                                     | 333 (3.47%)   | 275 (2.86%)              |
| Other vascular death                   | 226 (2.36%)   | 226 (2.35%)              |

a. Data from proposed Plavix label, submitted 11.3.97 to the Division of Cardio-Renal Drug Products.

## 19.0 Appendix Seven: Efficacy Summary for Reopro, Integrilin, and Plavix

### CAPRIE Trial (cont)

For the primary endpoint (time to occurrence of new ischemic stroke, new myocardial infarction, or other vascular death) the incidence curves separated early for the ASA and clopidogrel groups, with fewer events per time occurring in the clopidogrel group (data not shown) out to three years of follow-up.

### C. Integrilin (eptifibatide)

Eptifibatide has been submitted for approval to the Division of Cardio-Renal Drug Products (NDA 20-718). The two efficacy trials for eptifibatide in the treatment of UAPMQWMI were the PURSUIT Study (Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) and the IMPACT-II trial (Integrilin to Mimimize Platelet Aggregation and Coronary Thrombosis-II).

### PURSUIT Trial

This was a randomized, blinded, placebo-controlled trial in subjects with UAPMQWMI, comparing eptifibatide versus placebo. Study drugs were administered intravenously for up to 72 hours except when PTCA was performed, in which case the infusion could be extended for an additional 24 hours. All subjects additionally could receive heparin (90% of both groups received heparin). Subjects also were to receive ASA unless otherwise contraindicated (64% of both groups received ASA).

A major difference between this trial and the CAPTURE trial (above, using Abciximab) is that no scheduled angiogram was included in the protocol for PURSUIT. Per the sponsors...PURUIT study was a practice based, study designed to investigate the relative role of eptifibatide under all therapeutic strategies used in the therapy of UAP/NQWMI.'

The table below shows the incidence of the primary endpoint (incidence of death and/or MI at 30 days), along with incidence of the same endpoint at 3 and 7 days.

Table 19.0.5 Incidence of death and/or MI in the PURSUIT study<sup>a</sup>.

|                                          | Placebo <sup>c</sup><br>n=4697 | Eptifibatide <sup>c</sup><br>n=4680 | p value <sup>b</sup> |
|------------------------------------------|--------------------------------|-------------------------------------|----------------------|
| Death and/or MI at 3 days                | 427 (9.1%)                     | 356 (7.6%)                          | 0.009                |
| Death and/or MI at 7 days                | 550 (11.7%)                    | 472 (10.1%)                         | 0.012                |
| Death and/or MI at 30 days               | 743 (15.8%)                    | 667 (14.3%)                         | 0.034                |
| Death at 3 days                          | 58 (1.2%)                      | 41 (0.9%)                           | 0.091                |
| Death at 7 days                          | 95 (2.0%)                      | 69 (1.5%)                           | 0.044                |
| Death at 30 days                         | 177 (3.8%)                     | 164 (3.5%)                          | 0.495                |
| MI (both fatal and non-fatal) at 3 days  | 392 (8.4%)                     | 335 (7.2%)                          | 0.032                |
| MI (both fatal and non-fatal) at 7 days  | 491 (10.5%)                    | 437 (9.3%)                          | 0.071                |
| MI (both fatal and non-fatal) at 30 days | 642 (13.7%)                    | 589 (12.6%)                         | 0.121                |

a From NDA 20-718, volume 2.47, table 7-1.

b. p value calculated per the sponsor using Pearson's chi-square test.

c. 90% and 64% of the subjects in both groups received heparin and ASA respectively.

### IMPACT-II Trial

The IMPACT-II trial was a randomized, blinded, placebo-controlled trial in subjects with UAPMQWMI undergoing elective, urgent, or emergency coronary intervention (PTCA or atherectomy). IMPACT-II compared three groups: eptifibatide (two different doses); and placebo. Infusion of heparin and study drug was started after vascular access was established, but before PTCA/ atherectomy, and continued for 20-24 hours after the procedure. All subjects additionally could receive heparin (90% of both groups received heparin), but it was recommended that the heparin be discontinued after the procedure was complete. Subjects also were to receive ASA unless otherwise contraindicated (64% of both groups received ASA).

The primary endpoint of the trial was the occurrence within 30 days of death, myocardial infarction, urgent or emergent repeat coronary intervention, urgent or emergent CABG, or index placement of intracoronary stent for abrupt closure, performed on an intent-to-treat population. The table below shows the results of an analysis of the primary endpoint analysis and its components. Also shown are the p value and odds ratio/ 95% Confidence interval, comparing the eptifibatide groups with placebo.

19.0 Appendix Seven: Efficacy Summary for Reopro, Integrilin, and Plavix

Table 19.0.6 Incidence of primary endpoint and its components in the IMPACT-II study<sup>a</sup>.

|                                         | Placebo<br>n=1328 | Eptifibatide<br>135/0.5<br>n=1349 | Statistics vs.<br>Placebo <sup>d</sup> | Eptifibatide<br>135/0.75<br>n=1333 | Statistics vs.<br>Placebo <sup>d</sup> |
|-----------------------------------------|-------------------|-----------------------------------|----------------------------------------|------------------------------------|----------------------------------------|
| Composite Primary<br>Endpoint (30 days) | 151<br>(11.4%)    | 124 (9.2%)                        | p value =0.063<br>0.79 (0.6-1.01)      | 132 (9.9%)                         | p value =0.22<br>0.86 (0.67-1.10)      |
| Death                                   | 15 (1.1%)         | 7 (0.5%)                          | p value =0.13<br>0.80 (0.60-<br>1.07)  | 11 (0.8%)                          | p value =0.27<br>0.85 (0.64-1.13)      |
| MI                                      | 107 (8.1%)        | 89 (6.6%)                         |                                        | 92 (6.9%)                          |                                        |
| Death/ MI                               | 112 (8.4%)        | 93 (6.9%)                         |                                        | 97 (7.3%)                          |                                        |
| CABG                                    | 37 (2.8%)         | 22 (1.6%)                         |                                        | 27 (2.0%)                          |                                        |
| PTCA                                    | 37 (2.8%)         | 35 (2.6%)                         |                                        | 38 (2.9%)                          |                                        |
| Stent for abrupt closure                | 18 (1.4%)         | 7 (0.5%)                          |                                        | 7 (0.5%)                           |                                        |

a. From IMPACT-II publication ( ).

b. p value calculated from published value.

c. MI was defined in several ways in the trial. Data shown is for CPK  $\geq 3X$  over baseline.

d. Shown in p-value and odds ratio/ 95%CI (in bold).

**D. Comparison of procedures in trials in subjects with AUP/NQWMI**

Several of the trials discussed above recruited from the same population included as the PRISM and PRISM-PLUS trials in the current NDA (UAPMQWMI). A significant difference between the trials had to do with the timing and frequency of cardiac interventions. The percentages of subjects undergoing cardiac procedures during the first 30 days following initiation of study drug, in trials involving subjects with UAP/NQWMI are shown below. The RESTORE trial, also part of the tirofiban NDA, is included. The CAPRIE trial (clopidogrel) is not included, as it studied a different patient population (subjects with recent MI or stroke, or those with established peripheral arterial disease). EPILOGUE is also not included, as it excluded subjects with UAP/NQWMI.

Note that the subjects in the PURSUIT, PRISM and PRISM-PLUS trials had a much lower incidence of angioplasty, and a higher incidence of CABG, than did the EPIC, CAPTURE, and RESTORE trials. In the latter three trials, all subjects underwent both angiography and PTCA per protocol, while in the former three trials the subjects were followed for need for PTCA and other cardiac interventions.

Table 19.0.7 Incidence of specific cardiac procedures in the EPIC, CAPTURE, PURSUIT, IMPACT-II, PRISM, PRISM-PLUS, and RESTORE trials<sup>a</sup>.

| Study                                            | Angiography  | Angioplasty               | Atherectomy | CABG                   | Stent placement        |
|--------------------------------------------------|--------------|---------------------------|-------------|------------------------|------------------------|
| EPIC <sup>b</sup><br>(Abciximab, n=2099)         | 1994 (95)    | 1889 (90%)                | 105 (5%)    | 58 (2.8%) <sup>b</sup> | 20 (0.9%) <sup>b</sup> |
| CAPTURE <sup>a</sup><br>(Abciximab, n=1235)      | 1235 (100%)  | 1134 (91.3%) <sup>c</sup> | N/A         | 30 (2.4%) <sup>c</sup> | N/A                    |
| PURSUIT <sup>d</sup><br>(eptifibatide, n=9377)   | 6037 (64%)   | 2409 (26%)                | See note e  | 1449 (15.4%)           | See note e             |
| IMPACT-II <sup>f</sup><br>(eptifibatide, n=4010) | 3866 (96.9%) | 3681 (91.7%)              | 537 (13.4%) | 86 (2.1%)              | 163 (4.1%)             |
| PRISM <sup>f</sup><br>(tirofiban, n=3232)        | 2003 (62%)   | 654 (20.2%)               | 21 (0.64%)  | 565 (17.5%)            | N/A                    |
| PRISM-PLUS <sup>g</sup><br>(tirofiban, n=1915)   | 1729 (90.2%) | 590 (30.1%)               | 16 (0.80%)  | 482 (25.2%)            | 143 (7.5%)             |
| RESTORE <sup>h</sup><br>(tirofiban, n=2140)      | 2140 (100%)  | 1980 (92%)                | 159 (7.4%)  | 132 (6.2%)             | 175 (8.2%)             |

a. Data from (2), from Reopro package insert and from NDA-20-912 (tirofiban).

b. In the EPIC trial, entry into the trial required that subjects undergo PTCA and/or atherectomy. The CABG and stent placement data is from emergent need for these procedures within the first 30 days after study drug administration (see I).

c. The CAPTURE trial enrolled subjects following angiography with an identified lesion amenable to angioplasty. The angioplasty or other cardiac intervention was to be done after 18-24 hours of drug therapy. Number shown is for the successful PTCA events, out of the 1241 subjects (98.1%) of subjects had PTCA attempted, per protocol. The CABG data is for the first 30 days.

d. The data for the PURSUIT trial is taken at the end of 30 days (bottom row, from NDA 20-718, volume 2.47, table 6-10).

e. The PURSUIT trial collected PTCA, atherectomy and stent placement into one category: percutaneous intervention.

f. PRISM data is shown for first 30 day after start of study drug (see NDA 20-718, volume 2.47, section 6.2.2).

g. PRISM-PLUS data is shown for first 30 day after start of study drug (see NDA 20-Y 12, volume 1.42, section 3, table 23).

h. RESTORE shown for initial procedure, as all subjects underwent angiography  $\pm$  PTCA/atherectomy (NDA 20-912, vol. 1.55, table I1).

i. Data shown is for the initial procedures performed in the IMPACT-II trial. An additional 110 subjects had emergency PTCA and 32 had stent placement for abrupt closure during the initial 30 days after entry into trial.

## 20.0 Appendix **Eight:Choice** of Tirofiban Dose for Phase III Studies

### **20.0** Choice Of Tirofiban Dose Used In The Phase II-III Trials

The sponsor selected the appropriate dosing regimen of tirofiban to be used in the Phase III studies based on three general objectives: (1) finding a dosing regimen of tirofiban alone that would achieve a high level of inhibition of *ex vivo* platelet aggregation (to 5  $\mu$ M ADP as an agonist) consistently across the study population without significantly increasing bleeding events; (2) finding a dosing regimen of tirofiban that could achieve high levels of platelet inhibition yet be used safely in combination with heparin; and (3) determining a dosing regimen for tirofiban to be used when initiated in the setting of PTCA. The Phase II clinical development program was designed to provide information to address these questions.

#### Tirofiban When Used Alone

The initial target dosing regimen using tirofiban alone (in combination with aspirin) was developed for the first Phase II unstable angina study (Protocol **005**), and was based on previous experience with the investigational drug MK-0852, a cyclic **peptide GP IIb/IIIa inhibitor**(11). The **findings** in this early study in subjects with unstable angina suggested that moderate levels of platelet inhibition (55% median) were not adequate to prevent refractory cardiac ischemia in these subjects compared to subjects receiving standard care with heparin. Although this early study was not powered to be able to show a significant difference in the incidence of clinical events between treatment groups (77 subjects total in three groups), when median platelet inhibition was  $\geq 75\%$ , MK-0852 appeared to **decrease** refractory angina in unstable angina subjects receiving this drug compared to subjects receiving heparin.

Based on these results, protocol **#005** investigated three dosing regimens over three durations of **tirofiban** infusion in subjects with unstable angina. The respective regimens were designed to rapidly achieve increasing levels of platelet inhibition with a **30-minute** loading infusion and maintain that level of inhibition for the subsequent 47.5 hours (total duration of therapy was 48 hours, see section 6.1.1 for review). The initial loading/maintenance regimen chosen for Protocol 005 had been previously studied in subjects with stable coronary disease (protocol 004, reviewed by Dr. **Pellayo**) and had been found to achieve a median platelet inhibition of 74% and bleeding times of **1.9X-control** after a **6-hour** of tirofiban given with aspirin. The dosing regimens were studied in a sequential-panel design, such that the decision to progress to the next dosing regimen was made only **after** review of **pharmacodynamic** activity and adverse experiences.

Table 20.0.1 Doses of tirofiban used in protocol **#005** and mean plasma concentrations at the end of **24** hours<sup>a</sup>.

| Loading dose of tirofiban (over 30 minutes) | 47.5 hour infusion                    | Mean plasma concentration after 24 hours |
|---------------------------------------------|---------------------------------------|------------------------------------------|
| <b>0.3 <math>\mu</math>g/kg/min</b>         | <b>0.075 <math>\mu</math>g/kg/min</b> | <b>33.48<math>\pm</math>10.3</b>         |
| <b>0.4 <math>\mu</math>g/kg/min</b>         | <b>0.10 <math>\mu</math>g/kg/min</b>  | <b>48.6<math>\pm</math>17.1</b>          |
| <b>0.5 <math>\mu</math>g/kg/min</b>         | <b>0.15<math>\mu</math>g/kg/min</b>   | <b>69.0f20.4</b>                         |

a. Data from NDA volume 1.37, table D-2.

Table 20.0.2 Mean inhibition of platelets aggregation and bleeding time extension with varying doses of tirofiban in protocol **#005**<sup>a</sup>.

| Infusion duration | <b>0.30/0.075</b> group<br>n=28 | <b>0.4/0.1</b> group<br>n=23 | <b>0.6/0.15</b><br>n=20 |
|-------------------|---------------------------------|------------------------------|-------------------------|
| 30 minutes        | <b>90.0%</b>                    | <b>89.6%</b>                 | <b>96.0%</b>            |
| <b>24</b> hours   | <b>88.2%/ 2.2 mins</b>          | <b>82.9%/ 2.2 mins</b>       | <b>93.6%/ 3.9 mins</b>  |
| <b>48</b> hours   | <b>78.3%/ 2.6 mins</b>          | <b>86.3%/ 2.6 mins</b>       | <b>92.1%/ 3.3 mins</b>  |

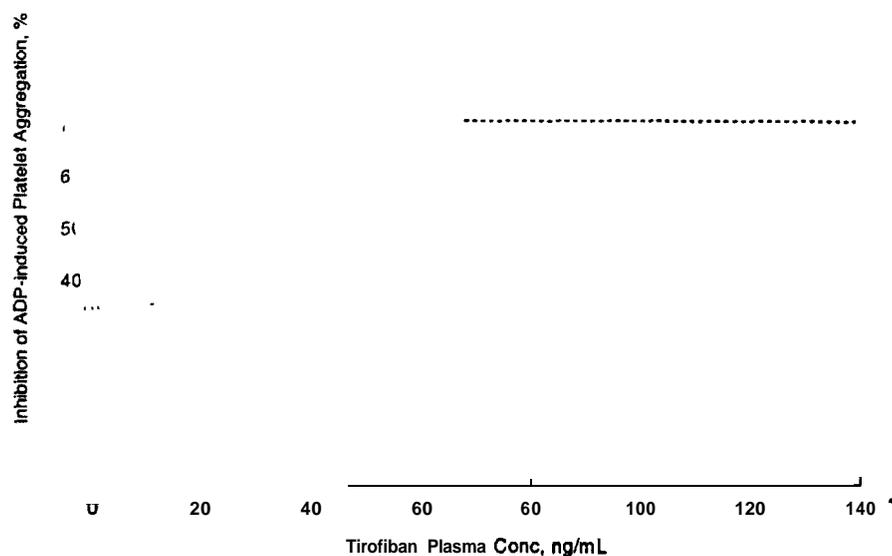
a. Data from NDA volume 1.37, table D-3, see section 6.1.1 for details.

## 20.0 Choice Of Tirofiban Dose Used In The Phase II-III Trials (cont)

The most consistent inhibition of platelet aggregation was achieved at the highest tirofiban dosing regimen: 95% of subjects were inhibited >70% at 48 hours in the (0.6/0.15) group compared to 74% of subjects in the (0.4/0.10) group, and 68% of subjects in the (0.3/0.075) group.

The sponsor also plotted the concentration/inhibition of platelet aggregation (IPA) relationship for the various doses of tirofiban used in each of the phase III studies. As before, the most consistent inhibition was obtained at the highest dosing regimen.

Figure 20.0.1 Concentration/IPA relationship for Tirofiban vs. IPA across all Phase II-III studies.



Panel 1: 0.3  $\mu\text{g}/\text{kg}/\text{min}$  for 30 min followed by 0.075  $\mu\text{g}/\text{kg}/\text{min}$  for 47.5 hr ( $\square$ ).

Panel 2: 0.4  $\mu\text{g}/\text{kg}/\text{min}$  for 30 min followed by 0.1  $\mu\text{g}/\text{kg}/\text{min}$  for 47.5 hr ( $\circ$ ).

Panel 3: 0.6  $\mu\text{g}/\text{kg}/\text{min}$  for 30 min followed by 0.15  $\mu\text{g}/\text{kg}/\text{min}$  for 47.5 hr ( $\blacktriangle$ )

Solid line is the fitted curve to the sigmoid-E<sub>max</sub> model

There were few clinical events study (see section 6.1. I), including no discontinuations due to bleeding, and the sponsor chose the highest dosing regimen studied (0.6/0.15) for use in the phase III studies when tirofiban was administered alone (PRISM-PLUS & PRISM trials).

## 20.0 Choice Of **Tirofiban** Dose Used In The Phase II-III Trials (cont)

### Tirofiban Used in Combination With Heparin

Protocol 008 (reviewed in section 6.1.6.3) was specifically designed to study the **pharmacodynamics** and safety of tirofiban in combination with heparin in subjects with unstable angina. The two highest dosing **regimens** from protocol #005 were chosen for this study in combination with heparin: a 30-minute loading infusion of 0.4  $\mu\text{g}/\text{kg}/\text{min}$  followed by a 47.5-hour maintenance infusion of 0.1  $\mu\text{g}/\text{kg}/\text{min}$  (0.4/0.1), and a 30-minute loading infusion of 0.6  $\mu\text{g}/\text{kg}/\text{min}$  followed by a 47.5-hour maintenance infusion of 0.15  $\mu\text{g}/\text{kg}/\text{min}$  (0.6/0.15). Heparin was given as a 5000 U bolus (where applicable) followed by a maintenance regimen of 1000 U/hour titrated to maintain the activated partial thromboplastin time (**aPTT**) 1.5- to 2X-control. These combination regimens were used to characterize the pharmacokinetic and **pharmacodynamic effects** of the presence of heparin on tirofiban as well as the safety profile of this combination therapy.

Heparin appeared to have no **effect on** the systemic plasma **clearance** of tirofiban. Concomitant **heparin also** did not appear to affect the percent of inhibition of platelet aggregation (**IPA**) by tirofiban. However, heparin appeared to have an additional effect on bleeding time, resulting in a greater proportion of subjects with observed **bleeding times >30 minutes**, especially at the higher dose. Though the overall incidence of bleeding events was comparable between tirofiban plus heparin and placebo plus heparin, **3/36 subjects (8%) were discontinued in the tirofiban plus heparin group due to mild bleeding from multiple sites (2/15 (13%) were in the high-dose group)**. In comparison, there had been no discontinuations due to bleeding in the study of tirofiban alone (see protocol #005, section 6.1.1). Given the additional effect of tirofiban plus heparin on bleeding time, and on discontinuations due to bleeding, the sponsor proposed using a lower dose when combination therapy was employed.

This concept was supported by the findings of protocol #007 (reviewed in section 6.1.2), which studied tirofiban in combination with heparin in the setting of coronary **angioplasty**. In this study, three regimens were also studied: (1) a bolus infusion given over 5 minutes of 5  $\mu\text{g}/\text{kg}$  followed by a maintenance infusion of 0.05  $\mu\text{g}/\text{kg}/\text{min}$ , (2) a bolus of 10  $\mu\text{g}/\text{kg}$  followed by an **infusion** of 0.1  $\mu\text{g}/\text{kg}/\text{min}$  and (3) a bolus of 10  $\mu\text{g}/\text{kg}$  followed by an infusion of 0.15  $\mu\text{g}/\text{kg}/\text{min}$ . The two highest maintenance infusions were the same maintenance **infusions** as the highest maintenance infusion regimens used in protocols 005 and 008, which resulted in a median **IPA** of 93 to 96%. **High-dose heparin (>10,000 U)** was given in the catheterization laboratory at the discretion of the physician and followed by a maintenance infusion (see section 6.1.2). Both the **tirofiban** and heparin infusions continued simultaneously for up to 24 hours. As was seen previously, concomitant heparin did not appear to affect the median percent **IPA**. A higher % of bleeding times, however, were markedly extended ( **$\geq 30$  minutes**) when measured shortly after concomitant administration of high-dose heparin and tirofiban. Bleeding events were primarily minor events related to the catheterization procedure and were observed equally across the treatment groups. Non-catheter-site bleeding was also comparable across treatment groups, except for oropharyngeal **bleeding/hemoptysis**, which was clearly increased in the group receiving the 0.15  $\mu\text{g}/\text{kg}/\text{min}$  maintenance infusion (23% of subjects experienced bleeding at this site). There was also a high rate of discontinuations in the high-dose group; most of these discontinuations were either directly or indirectly related to bleeding. This suggested that increased bleeding might be a concern when high-dose tirofiban (e.g., a maintenance infusion of 0.15  $\mu\text{g}/\text{kg}/\text{min}$ ) was given with concomitant high-dose heparin. These findings, together with the **findings** of protocol 008, formed the basis of the initial decision to use the maintenance regimen of 0.1  $\mu\text{g}/\text{kg}/\text{min}$  in subjects with unstable angina when tirofiban was used in combination with heparin (in the **PRISM-PLUS** trial). The corresponding loading **infusion** of 0.4  $\mu\text{g}/\text{kg}/\text{min}$  for 30 minutes, which had been studied in the unstable angina protocols, #005 and #008, was also chosen, as this regimen had been shown to achieve plasma concentrations of tirofiban and median **IPA** at 30 minutes that were consistent with levels seen with the 0.1  $\mu\text{g}/\text{kg}/\text{min}$  maintenance infusion at 24 and 48 hours.

## 20.0 Appendix Eight: Choice Of **Tirofiban** Dose Used In The Phase II-III Trials

### Tirofiban in Combination with Heparin in the Setting of PTCA (RESTORE Trial)

Based on the discussion above, the initial regimen proposed for the RESTORE trial of tirofiban in the setting of angioplasty was a bolus of 10  $\mu\text{g}/\text{kg}$ , followed by a maintenance infusion 0.1  $\mu\text{g}/\text{kg}/\text{min}$ . This bolus dose was the same as used in protocol #007, and the maintenance dose was the same chosen for the use with tirofiban alone. Subsequently, however, preliminary data of a small trial with abciximab suggested that bleeding complications could be reduced by decreasing the amount of heparin given during angioplasty, then stopping heparin immediately after angioplasty, pulling the femoral sheaths once the heparin **effect** had worn **off**(12). This trial suggested that this could be done safely with the GP IIb/IIIa inhibitor still continuing at high levels of platelet inhibition. This data suggested that an alternate regimen for use in angioplasty would be to give an initial bolus of 10  $\mu\text{g}/\text{kg}$  of tirofiban followed by a maintenance infusion of 0.15  $\mu\text{g}/\text{kg}/\text{min}$  (the highest **tirofiban** maintenance regimen studied in protocol #007), since heparin would be expected to be discontinued immediately after the procedure and would not be administered concomitantly for most of the tirofiban infusion. This, in fact, was the strategy that ultimately was used for dosing tirofiban in the setting of angioplasty (RESTORE trial).

### Duration of Infusions

The **final** consideration for the dosing regimens for the Phase III studies was the duration of the infusions in the respective studies, for which little data exists. Some data suggest that platelet adhesion, aggregation and **thrombus** formation are largely completed within the first 24 hours **after** clinical presentation, while other data suggest that **thromboxane** elevation (as both a marker of **endothelial** injury and platelet aggregation) only returns to **baseline** by 96 hours. Recommendations for treatment of unstable angina with the combination of aspirin and heparin range from 2 to 6 days( 13, 14). From the data with **abciximab** (1), a bolus infusion was not sufficient to reduce acute cardiac ischemic events related to thrombotic occlusion of the treated coronary vessel after angioplasty. In the EPIC trial, an additional 12-hour infusion of abciximab was required. With the bolus plus infusion regimen of abciximab, high levels of platelet inhibition were sustained throughout the infusion and the antiplatelet **effect** persisted, along with elevated bleeding times, to at least 24 hours. **The** efficacy of **abciximab** in preventing recurrent coronary events was summarized in appendix 7, section 19.0.

## 20.0 Appendix Eight: Choice Of **Tirofiban** Dose Used In The Phase II-III Trials (cont)

### Duration of Infusions (cont)

The sponsor concluded that prolonged antiplatelet activity is important for reducing cardiac ischemic events, at least after angioplasty. The duration of the infusions for the Phase III studies was based on the general principle that antiplatelet activity should be maintained as long as possible given the practice paradigms for each of the respective studies. For example, in PRISM, the key objective was to study tirofiban alone for medical stabilization of subjects, unconfounded by concomitant cardiac procedures. Since an “early invasive” strategy (of catheterization and angioplasty, within 48 hours) is often favored for management of subjects with UAP/NQWMI, 48 hours represented the upper limit of the time before performing invasive procedures. Therefore, this infusion duration was chosen for the PRISM study and the **48-hour** time point; the end of the infusion was chosen as the time of primary endpoint for the trial.

In the PRISM-PLUS trial, a **48-hour** drug infusion for medical stabilization was chosen to correspond to the PRISM study, but administration of tirofiban was allowed to be continued through **angiography** and angioplasty, so the infusion duration was not limited by the constraints imposed by the PRISM study design. Thus, in PRISM-PLUS, the tirofiban infusion could be continued for varying times after the initial **48-hour** period for up to 108 hours; this also allowed subjects to have a minimum of 12 and a maximum of 24 hours of study drug after completion of an angioplasty.

In the RESTORE trial, tirofiban was initiated just prior to commencing either balloon inflation or atherectomy, rather than for an extended period prior to the procedure (as was the case in PRISM and PRISM-PLUS). To try to maintain prolonged high-level platelet inhibition to at least a comparable duration as abciximab, the sponsor decided to infuse tirofiban for 36 hours **after** the procedure. This also represented the upper limit of practice patterns in which subjects are usually discharged within 1 to 2 days after a successful PTCA/ angioplasty.

### Final Regimens Used in the Phase III Trials

In summary, the estimated highest, safe dose that had consistent inhibition across the population was chosen for the respective Phase III studies. These regimens are shown in 20.0.3. Note that in PRISM-PLUS, the infusion regimen of tirofiban was decreased for use in combination **with** heparin, compared to tirofiban administered alone. In RESTORE, the higher regimen was used again since it was expected that **heparin** use would be limited to the catheterization **laboratory and** that after sheath removal, tirofiban **would** be continued alone for the duration of the infusion. The subjects in the RESTORE trial also received the bolus over 3, instead of 30, minutes. In addition, all subjects received concomitant aspirin (generally 300 to 325 mg q.d. during the study drug infusion period), unless contraindicated. Except in the setting of angioplasty where high-dose heparin was administered as **boluses** in the catheterization laboratory, consistent with local guidelines, heparin was initiated as a 5000 U bolus followed by a maintenance infusion of 1000 U/hour that was then titrated to maintain the **aPTT** at **1.5-** to 2X-control.

Table 20.0.3 The three phase III trials submitted in the NDA utilized three separate dosing regimens for tirofiban, as seen in the table below.

| Trial      | Design (arms)                                           | Tirofiban Regimen                                                                                                                                                                                                                                  | Heparin Regimen                                                                                      |
|------------|---------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| PRISM      | 1. <b>Tirofiban</b><br>2. Heparin                       | 0.6 $\mu\text{g}/\text{kg}/\text{min}$ loading dose (30 mins.)<br>0.15 $\mu\text{g}/\text{kg}/\text{min}$ maintenance                                                                                                                              | 5000 Unit (U) bolus<br>1000 U/hr infusion with adjustment as needed                                  |
| PRISM-PLUS | 1. Tirofiban<br><br>2. Tirofiban +Heparin<br>3. Heparin | 0.6 $\mu\text{g}/\text{kg}/\text{min}$ loading dose (30 mins.)<br>0.15 $\mu\text{g}/\text{kg}/\text{min}$ maintenance<br><br>0.4 $\mu\text{g}/\text{kg}/\text{min}$ loading dose (30 mins.)<br>0.10 $\mu\text{g}/\text{kg}/\text{min}$ maintenance | None<br><br>5000 U bolus<br>1000 U/hr infusion with adjustment as needed                             |
| RESTORE    | 1. <b>Tirofiban(+Heparin)*</b><br>2. Placebo (+Heparin) | 10 $\mu\text{g}/\text{kg}$ loading dose, (3 mins.)<br>0.15 $\mu\text{g}/\text{kg}/\text{min}$ maintenance                                                                                                                                          | 10,000 U bolus<br>(150 $\mu\text{g}/\text{kg}$ if subject <70 kg)<br>No infusion after PTCA complete |

a. Per protocol, all subjects in the RESTORE trial received open-label heparin during the angiography/PTCA.

21.0 Appendix Nine: Abnormal **LFTs** in the phase III trials of tirofiban

At the reviewer's request, the sponsor also submitted information about the height of the abnormal **LFTs**, and their association with clinical **AEs**. The sponsor focused on ALT, alk phos and total bilirubin as markers. The listing below shows all subjects in the phase III trials who had at elevation in at least 2 of the three LFTs of interest (ALT, bilirubin, or alk phos), with one  $\geq 2X$  above normal. A larger number of subjects had lesser elevations (data not shown). These subjects were also examined by the medical officer, and any subjects with a striking elevation of only one LFT value (i.e., ALT) were also included. The table also shows the occurrence of clinical **AEs** potentially related to hepatic injury (anorexia, hepatomegaly, cholelithiasis, cholecystitis, jaundice, pruritus, skin discoloration) or bleeding complications, along with the **LFTs** in those subjects. The lab values are shown as the fold-increase above upper limit of normal. Subjects in bold have extreme elevations in one or more of the lab values.

Table 21.0.1 Listing of subjects with both ALT and Bilirubin  $\geq 2X$  upper limit of normal, along with presence of bleeding complication, clinical AE linked to liver dysfunction<sup>a</sup>.

| Treatment Group & Subjectk                     | ALT   | Alk Phos | Bilirubin | Bleeding Comp <sup>b</sup> | Clinical AE                |
|------------------------------------------------|-------|----------|-----------|----------------------------|----------------------------|
| <b>Tirofiban + Heparin Group</b><br>PRISM-PLUS |       |          |           |                            |                            |
| AN 6994                                        | 1.79  | 1.42     | 2.39      |                            |                            |
| AN 1620                                        | 2.28  | 1.88     | 1.38      | TIMI Major                 | Pruritus (at hr 68)        |
| AN 1072                                        | 2.32  | 2.32     | 0.33      |                            |                            |
| AN 7068                                        | 2.30  | 0.64     | 1.04      |                            |                            |
| AN 5355                                        | 4.97  | 1.74     | 0.25      |                            |                            |
| AN 6329                                        | 3.65  | 1.04     | 0.33      | Y                          |                            |
| AN 6915                                        | 3.74  | 0.93     | 1.81      |                            |                            |
| AN 6899                                        | 8.76  | 1.59     | 0.33      |                            |                            |
| AN 7752                                        | 2.91  | 0.45     | 1.17      |                            |                            |
| AN 1185                                        | 3.89  | 0.79     | 1.08      |                            |                            |
| <b>RESTORE</b>                                 |       |          |           |                            |                            |
| AN 1990                                        | 3.66  | 0.70     | 2.67      |                            |                            |
| AN 3015                                        | 0.52  | ND       | 4         |                            | Pruritus                   |
| AN 2103                                        | 5.61  | 3.00     | 1         |                            |                            |
| AN 2395                                        | 1.9   | 0.46     | 5.5       |                            |                            |
| AN 2172                                        | 2.68  | 1.31     | 0.2       |                            |                            |
| AN 5279                                        | 2.95  | 1.01     | 0.76      | Y                          |                            |
| AN 3815                                        | ND    | 2.2      | 1         | Y                          |                            |
| AN 5151                                        | 15.52 | 2.05     | 0.77      |                            |                            |
| AN 3731                                        | 0.51  | 0.84     | 6.3       |                            |                            |
| <b>Yeparin Alone Group</b><br>PRISM-PLUS       |       |          |           |                            |                            |
| AN 6016                                        | 1.29  | 0.81     | 2.42      |                            |                            |
| AN 1096                                        | 2.71  | 1.09     | 1.04      |                            |                            |
| AN 6521                                        | 3.41  | 1.03     | 0.47      |                            |                            |
| AN 6936                                        | 3.58  | 1.25     | 0.57      |                            |                            |
| AN 1082                                        | 2.08  | 0.78     | 1.14      |                            |                            |
| AN 665 1                                       | 1.68  | 0.50     | 2.38      |                            | Hepatic insufficiency, SAE |
| AN 6188                                        | 2.14  | 1.28     | 0.42      |                            |                            |
| AN 7066                                        | 59.77 | 0.52     | 1.24      | Y                          |                            |
| AN 1643                                        | 3.79  | 1.08     | 0.43      |                            |                            |
| AN 6113                                        | 2.08  | 0.04     | 1.81      | Y                          | Cholelithiasis             |
| AN 6334                                        | 2.46  | 1.03     | 0.42      |                            |                            |
| AN 6888                                        | 5.13  | 0.55     | 1.81      |                            |                            |
| AN 1154                                        | 3.54  | 1.07     | 0.38      |                            |                            |
| AN 7609                                        | 5.79  | 0.5      | 2.17      |                            |                            |
| AN 7751                                        | 17.37 | 0.68     | 1.08      |                            |                            |
| AN 1445                                        | 3.32  | 1.07     | 0.33      |                            |                            |
| AN 1166                                        | 2.86  | 1.03     | 0.666     |                            |                            |

21.0 Appendix Nine: Abnormal LFTs in the phase III trials of tirofiban (cont)

Table 21.0.1 Listing of subjects with both ALT and Bilirubin  $\geq 2X$  upper limit of normal, along with presence of bleeding complication and clinical AE linked to liver dysfunction<sup>a</sup>.

| Treatment Group & Subject #  | ALT   | Alk Phos | Bilirubin | Bleeding Comp <sup>b</sup> | Clinical AE        |
|------------------------------|-------|----------|-----------|----------------------------|--------------------|
| <b>Heparin-Alone Group</b>   |       |          |           |                            |                    |
| RESTORE                      |       |          |           |                            |                    |
| AN 3893                      | 2.17  | 0.65     | 1.33      | Y                          |                    |
| AN 4833                      | 10.28 | 1.69     | 3.04      |                            |                    |
| AN 6440                      | 4.21  | 1.31     | 0.33      |                            |                    |
| AN 2390                      | 8.14  | 0.38     | 0.666     |                            |                    |
| AN 2975                      | 41.7  | 0.991    | 2         |                            |                    |
| AN 3836                      | 3.63  | 1.06     | 1.38      |                            |                    |
| AN 6551                      | 2.2   | 1.11     | 0.66      |                            |                    |
| AN 6835                      | 6.60  | 1.39     | 0.666     |                            |                    |
| AN 2378                      | 1.13  | 0.38     | 2         | Y                          |                    |
| AN3259                       | 0.85  | 7.22     | 0.7       | Y                          |                    |
| AN 1120                      | 3.34  | 1.55     | 0.54      |                            |                    |
| AN 1378                      | 13.12 | 1.09     | 0.75      |                            |                    |
| AN 2705                      | 3.13  | 1.27     | 0.61      |                            |                    |
| AN 1246                      | 2.9   | 1.3      | 0.33      |                            |                    |
| AN 3100                      | 2.07  | 1.07     | 0.2       |                            |                    |
| AN 1992                      | 7.54  | 1.46     | 0.58      |                            |                    |
| AN 2886                      | 1.84  | 2.38     | 0.41      |                            |                    |
| AN 1646                      | 3.17  | 0.91     | 5.61      |                            |                    |
| AN 1317                      | 9.45  | 1.72     | 0.5       |                            |                    |
| AN 1208                      | 0.34  | 0.88     | 4.83      |                            |                    |
| AN 1889                      | 2.85  | 1.03     | 0.54      | Y                          |                    |
| AN 5647                      | 1.08  | 0.66     | 2.58      |                            | Pruritus at 35 hrs |
| <b>Tirofiban Alone Group</b> |       |          |           |                            |                    |
| PRISM-PLUS                   |       |          |           |                            |                    |
| AN 6625                      | 1.42  | 0.6      | 2.28      | TIMI Major                 |                    |
| AN 7490                      | 1.51  | 2.64     | 0.5       |                            |                    |
| AN 1635                      | 2.75  | 1.24     | 0.91      |                            |                    |
| AN 4616                      | 12.23 | 1.02     | 2.08      |                            |                    |
| AN 3106                      | 4.53  | 1.93     | 0.81      |                            |                    |
| AN 4401                      | 2.09  | 0.75     | 1.09      |                            |                    |
| AN 4974                      | 29.69 | 1.99     | 0.42      |                            |                    |
| AN 2807                      | 3.91  | 1.21     | 0.66      |                            |                    |
| AN 3659                      | 2.05  | 0.48     | 1.14      |                            |                    |
| AN 5705                      | 2.53  | 2.59     | 0.66      |                            |                    |
| AN 4678                      | 9.53  | 0.8      | 2         |                            |                    |
| AN 7866                      | 1.24  | 1.24     | 3.83      |                            |                    |

a. Data from sponsor at request of medical reviewer. Data shown is selected from list of all subjects with  $\geq 2X$  increase in ALT, Alk phos or bilirubin with either clinical AE or bleeding complication, submitted by sponsor, not independently verified by FDA.

b. Bleeding complications were defined as either a bleeding episode that was moderate, severe, or life-threatening, or a TIMI major-bleeding event. If the subject had both types of bleeding, the table entry is Y-TIMI Major.

## 22.0 Appendix Ten: Comparability of baseline demographics for PTCA subgroup in the PRISM-PLUS, PRISM, and RESTORE trials

The sponsor examined a population similar to that of the RESTORE trial in the PRISM-PLUS and PRISM trials, in order to compare the occurrence of clinical events in subjects according to the receipt of PTCA. The analysis of this population is found in section 7.0.3.2. Below, the demographics of those subjects who underwent PTCA in PRISM-PLUS, PRISM, and RESTORE are compared.

### 22.0.1 Comparability of baseline demographics for the PTCA subgroup in the PRISM-PLUS, PRISM, and RESTORE trials

#### 22.0.1a Baseline demographics for the PTCA subgroup in the PRISM-PLUS, PRISM, and RESTORE trials

All three trials enrolled subjects with UAPMQWMI. In the RESTORE trial, these subjects were felt to be at high risk for cardiac events, and were sufficiently unstable to have undergone angiography, and to have an identified coronary artery lesion amenable to PTCA. In distinction, PRISM-PLUS and PRISM enrolled subjects who **were** watched closely, but in whom no cardiac **revascularization** was emergently indicated. In the PRISM-PLUS trial, all subjects were to undergo angiography at the end of 48 hours of study drug infusion. The RESTORE trial also entered subjects with Q-wave **MIs**, who were excluded **from** the PRISM-PLUS and PRISM trials.

The overall demographics of the three trials were reviewed in the respective 'Patient Demographics & Baseline Characteristics' sections of their individual reviews (6.1.2.12.1, 6.2.2.12.1, and 6.3.2.12.1). The three populations were similar in terms of age, sex, antecedent medical history (i.e., diabetes, hypertension), and other medications taken at time of entry into the trial. The three tables below summarize some of the **demographics for** the PRISM-PLUS, PRISM, and RESTORE trials.

There were some **differances** in terms of clinical presentation<sup>1</sup> First, PTCA subjects in the PRISM-PLUS had a higher incidence of ECG ischemia and NQWMI on presentation as compared to subjects undergoing PTCA **enrolled** in the PRISM study. In addition, the RESTORE study population included subjects presenting with S-T elevation **myocardial** infarctions ( the primary angioplasty cohort); such subjects were excluded in the other trials.

Second, while all three trials enrolled subjects with acute coronary syndrome, the duration of the acute coronary syndrome was up to 72 hours prior to study entry in the RESTORE trial, while it was 112 hours in the PRISM-PLUS trial, and **≤24** hours in the PRISM trial. This is reflected in the duration of time **from** onset of pain to start of study drug, which is shown below for the PRISM-PLUS and PRISM trials. No information is available as to the average duration of symptoms prior to entry into the RESTORE trial.

The next three tables summarize the demographics of the subjects who underwent PTCA in **the** three phase III trials. The table for the RESTORE trial shows the demographics of all subjects enrolled in the trial, since all **of** them underwent a per-protocol PTCA. They also show the percentage of each treatment group that received PTCA during the **first** 30 days (approximately **30%** in the PRISM-PLUS trial, and 20% in the PRISM trial).

**22.0.1a** Baseline demographics for the PTCA subgroup in the PRISM-PLUS, PRISM, and RESTORE trials (cont)

Table 22.0. 1a. 1 Demographics of PRISM-PLUS subjects who underwent PTCA during the initial hospitalization<sup>a,d</sup>.

| Attribute                 | Tirofiban<br>N=109/345<br>(31.5%) | Tirofiban<br>+ Heparin<br>N=239/773<br>(30.9%) | Heparin<br>N=236/797<br>(29.6%) | p-value<br>T+H vs. H |
|---------------------------|-----------------------------------|------------------------------------------------|---------------------------------|----------------------|
| Age (years)               |                                   |                                                |                                 | 0.87                 |
| < 35                      | 0 (0%)                            | 1 (0.4%)                                       | 1 (0.4%)                        |                      |
| 35-44                     | 10 (9.2%)                         | 20 (8.4%)                                      | 15 (6.4%)                       |                      |
| 45-54                     | 22 (20.2%)                        | 51 (21.3%)                                     | 50 (21.2%)                      |                      |
| 55-64                     | 33 (30.3%)                        | 71 (29.7%)                                     | 77 (32.6%)                      |                      |
| 65-74                     | 32 (29.4%)                        | 71 (29.7%)                                     | 65 (27.5%)                      |                      |
| ≥ 75                      | 12 (11.0%)                        | 25 (10.5%)                                     | 28 (11.9%)                      |                      |
| Mean Age (year ± SD)      | 61.3 ± 11.1                       | 61.0 ± 10.9                                    | 61.3 ± 11.2                     |                      |
| Gender                    |                                   |                                                |                                 | 0.44                 |
| Female                    | 44 (40.4%)                        | 83 (34.7%)                                     | 74 (31.4%)                      |                      |
| Male                      | 65 (59.6%)                        | 156 (65.3%)                                    | 162 (68.6%)                     |                      |
| Race                      |                                   |                                                |                                 | 0.91                 |
| Caucasian                 | 100 (91.7%)                       | 215 (90.0%)                                    | 216 (91.5%)                     |                      |
| Black                     | 2 (1.8%)                          | 8 (3.3%)                                       | 9 (3.8%)                        |                      |
| Hispanic                  | 7 (6.4%)                          | 11 (4.6%)                                      | 9 (3.8%)                        |                      |
| Other                     | 0 (0%)                            | 5 (2.1%)                                       | 2 (0.8%)                        |                      |
| Antecedent CAD            |                                   |                                                |                                 | 0.71                 |
| Diabetes                  | 67 (61.5%)                        | 135 (56.5%)                                    | 129 (54.7%)                     |                      |
| Hypertension              | 22 (20.2%)                        | 51 (21.3%)                                     | 51 (21.6%)                      | 0.99                 |
|                           | 48 (44.0%)                        | 125 (52.3%)                                    | 123 (52.1%)                     | 0.99                 |
| ECG Ischemia              | 104 (95.4%)                       | 220 (92.1%)                                    | 221 (93.6%)                     | 0.59                 |
| ST Depression             | 68 (62.4%)                        | 129 (54.0%)                                    | 133 (56.4%)                     | 0.64                 |
| T-Wave Inversion          | 61 (56.0%)                        | 123 (51.5%)                                    | 116 (49.2%)                     | 0.65                 |
| ST Elevation <sup>b</sup> | 19 (17.4%)                        | 49 (20.5%)                                     | 42 (17.8%)                      | 0.48                 |
| Presentation <sup>c</sup> |                                   |                                                |                                 | 0.90                 |
| Unstable Angina           | 64 (58.7%)                        | 134 (56.1%)                                    | 138 (58.5%)                     |                      |
| Possible NQWMI            | 33 (30.3%)                        | 70 (29.3%)                                     | 75 (31.8%)                      |                      |
| Evolving MI               | 12 (11.0%)                        | 35 (14.6%)                                     | 92 (9.7%)                       |                      |

a. PRISM-PLUS analyses include subjects with a PTCA during the initial hospitalization. T do not include subjects with a PTCA following a readmission.

b. Only subjects with transient ST elevation (<20 minutes in duration) were eligible for enrollment.

c. Subjects presenting with ST elevation myocardial infarction were not enrolled in the PRISM PLUS trial.

d. Data from sponsor at reviewer's request.

**22.0.1a** Baseline demographics for the PTCA subgroup in the PRISM-PLUS, PRISM, and RESTORE trials (cont)

Table 22.0.1a.2 Demographics of subjects in the PRISM trial who underwent PTCA<sup>a,d</sup>.

| Attribute                 | Heparin<br>N=334/1616<br>(20.5%) | Tirofiban<br>N=320/1616<br>(19.8%) | p-value |
|---------------------------|----------------------------------|------------------------------------|---------|
| Age (years)               |                                  |                                    | 0.52    |
| < 35                      | 1 (0.3%)                         | 1 (0.3%)                           |         |
| 35-44                     | 27 (8.1%)                        | 20 (6.2%)                          |         |
| 45-54                     | 77 (23.1%)                       | 63 (19.7%)                         |         |
| 55-64                     | 95 (28.4%)                       | 106 (33.1%)                        |         |
| 65-74                     | 98 (29.3%)                       | 96 (30.0%)                         |         |
| ≥ 75                      | 36 (10.8%)                       | 34 (10.6%)                         |         |
| Mean Age (year ± SD)      | 60.6 ± 11.2                      | 61.2 ± 10.7                        | 0.52    |
| Gender                    |                                  |                                    | 0.45    |
| Female                    | 109 (32.6%)                      | 95 (29.7%)                         |         |
| Male                      | 225 (67.4%)                      | 225 (70.3%)                        |         |
| Race                      |                                  |                                    | 0.26    |
| Caucasian                 | 284 (85.0%)                      | 289 (90.3%)                        |         |
| Black                     | 14 (4.2%)                        | 7 (2.2%)                           |         |
| Hispanic                  | 20 (6.0%)                        | 12 (3.8%)                          |         |
| Other                     | 16 (4.8%)                        | 12 (3.8%)                          |         |
| Antecedent CAD            | 231 (69.2%)                      | 218 (68.1%)                        | 0.80    |
| Diabetes                  | 80 (24.0%)                       | 61 (19.1%)                         | 0.15    |
| Hypertension              | 185 (55.4%)                      | 163 (50.9%)                        | 0.27    |
| ECG Ischemia <sup>b</sup> | 223 (66.8%)                      | 230 (71.9%)                        | 0.18    |
| ST Depression             | 87 (26.0%)                       | 96 (30.0%)                         | 0.30    |
| T-Wave Inversion          | 167 (50.0%)                      | 164 (51.3%)                        | 0.76    |
| ST Elevation              | 26 (7.8%)                        | 32 (10.0%)                         | 0.34    |
| Presentation <sup>c</sup> |                                  |                                    | 0.97    |
| Unstable Angina           | 249 (74.6%)                      | 237 (74.1%)                        |         |
| Possible NQWMI            | 61 (18.3%)                       | 52 (16.2%)                         |         |
| Evolving MI               | 24 (7.2%)                        | 31 (9.7%)                          |         |

a. PRISM analyses include all subjects with a PTCA, whether during the initial or following admission. It was not possible to identify the PTCA procedure as occurring during the initial hospitalization or following a readmission due to the design of the case report forms and the collection of this information in the database.

b. Only subjects with transient ST elevation (<20 minutes in duration) were eligible for enrollment.

c. Subjects presenting with ST elevation myocardial infarction were not enrolled in the PRISM PLUS trial.

d. Data from sponsor at reviewer's request.

**22.0.1a** Baseline demographics for the PTCA subgroup in the PRISM-PLUS, PRISM, and RESTORE trials (cont)

Table 22.0.1a.3 Demographics of subjects in the RESTORE trial<sup>a,d</sup>.

|                                              | Tirofiba<br>n=1071 |         | Placebo<br>n=1070 |         | p-value      |
|----------------------------------------------|--------------------|---------|-------------------|---------|--------------|
|                                              | n                  | %       | n                 | %       |              |
| <b>Age</b>                                   |                    |         |                   |         |              |
| <30 years                                    | 0                  | 0.0     | 3                 | 0.3     | 0.841        |
| 30 to 39 years                               | 43                 | 4.0     | 36                | 3.4     |              |
| 40 to 49 years                               | 185                | 17.3    | 198               | 18.5    |              |
| 50 to 59 years                               | 307                | 28.7    | 298               | 27.8    |              |
| 60 to 69 years                               | 316                | 29.5    | 319               | 29.8    |              |
| 70 to 79 years                               | 211                | 19.7    | 205               | 19.2    |              |
| 80 years or older                            | 9                  | 0.8     | 11                | 1.0     |              |
| <b>Age (years)</b>                           | <b>59±11.10</b>    |         | <b>59±11.0</b>    |         | <b>0.933</b> |
| <b>Gender</b>                                |                    |         |                   |         |              |
| Male                                         | 777                | 72.6    | 782               | 73.1    | 0.808        |
| Female                                       | 294                | 27.4    | 288               | 26.9    |              |
| <b>Race</b>                                  |                    |         |                   |         |              |
| Caucasian                                    | 943                | 88.1    | 962               | 89.9    | 0.146        |
| Black                                        | 70                 | 6.5     | 50                | 4.7     |              |
| Hispanic                                     | 42                 | 3.9     | 33                | 3.1     |              |
| Other                                        | 9                  | 0.8     | 16                | 1.5     |              |
| Asian                                        | 7                  | 0.7     | 9                 | 0.8     |              |
| <b>Inclusion Criteria</b>                    |                    |         |                   |         |              |
| Procedure preceded by:                       |                    |         |                   |         |              |
| Unstable angina                              | 726                | (67.8)  | 728               | (68.0)  | 0.769        |
| Acute M.I.                                   | 274                | (25.6)  | 279               | (26.1)  |              |
| Acute MI (primary PTCA)                      | 71                 | (6.6)   | 63                | (5.9)   |              |
| <b>ECG abnormalities (selected):</b>         |                    |         |                   |         |              |
| Myocardial infarction                        | 261                | (24.6)  | 255               | (23.9)  | 0.762        |
| Nonspecific ST-T change                      | 226                | (21.3)  | 229               | (21.5)  | 0.916        |
| ST segment depression                        | 140                | (13.2)  | 141               | (13.2)  | 1.000        |
| ST segment elevation                         | 192                | (18.0)  | 216               | (20.3)  | 0.205        |
| T-wave abnormality                           | 48                 | (4.5)   | 38                | (3.7)   | 0.273        |
| T-wave increased                             | 34                 | (3.2)   | 20                | (1.9)   | 0.055        |
| T-wave inversion                             | 353                | (33.2)  | 333               | (31.3)  | 0.354        |
| <b>Subjects with any secondary diagnoses</b> | 1071               | (100.0) | 1070              | (100.0) | 1.000        |
| Hypertension                                 | 575                | (53.7)  | 598               | (55.9)  | 0.318        |
| Diabetes mellitus                            | 210                | (19.6)  | 210               | (19.6)  | 1.000        |
| Myocardial infarction                        | 378                | (35.3)  | 367               | (34.3)  | 0.650        |
| Previous angina pectoris (unstable)          | 941                | (87.9)  | 933               | (87.2)  | 0.648        |
| Coronary bypass surgery                      | 68                 | (6.3)   | 86                | (8.0)   | 0.133        |
| PTCA                                         | 223                | (20.8)  | 213               | (19.9)  | 0.629        |
| Angina pectoris (stable/exertional)          | 282                | (26.3)  | 254               | (23.7)  | 0.178        |
| Peripheral vascular disease                  | 61                 | (5.7)   | 73                | (6.8)   | 0.286        |

**22.0.1b Comparability of concomitant therapies received in the PRISM-PLUS, PRISM, and RESTORE trials**  
**1. Cardiac procedures performed**

The populations of the three trials not similar in terms of the cardiac procedures each received, as summarized in the table below. Note that while fewer subjects in the PRISM trial had cardiac procedures than the subjects in PRISM-PLUS, a substantial fraction of them still received either angiography or angioplasty within the first 30 days (the cut-off for SAE reporting). Note also that the subjects in the PRISM-PLUS trial had far fewer angioplasties or atherectomies than the group in the RESTORE trial. RESTORE, in contrast, had fewer CABGs in the first 30 days.

Table 22.0.1 b. 1 (from table 8.0.4.7.1) Incidence of specific cardiac procedures within first 30 days of the PRISM, PRISM-PLUS, and RESTORE trials<sup>a</sup>.

| Study                                             | Angiography         | Angioplasty | Atherectomy | CABG        | Stent placement |
|---------------------------------------------------|---------------------|-------------|-------------|-------------|-----------------|
| <b>PRISM<sup>b</sup></b><br>(tirofiban, n=3232)   | 2003 (62%)          | 654 (20.2%) | 21 (0.64%)  | 565 (17.5%) | 222 (6.9%)      |
| PRISM-PLUS <sup>c</sup><br>(tirofiban, n=1915)    | <b>1730 (90.3%)</b> | 590 (30.1%) | 16 (0.80%)  | 482 (25.2%) | 143 (7.5%)      |
| <b>RESTORE<sup>d</sup></b><br>(tirofiban, n=2140) | <b>2140 (100%)</b>  | 1980 (93%)  | 159 (7.4%)  | 46 (2.2%)   | 175 (8.2%)      |

a. Data from individual study summaries and electronic datasets, NDA-20-912, and from sponsor.

b. PRISM data is shown for first 30 day after start of study drug (see NDA 20-718, volume 2.47, section 6.2.2).

c. PRISM-PLUS data is shown for first 30 day after start of study drug (see NDA 20-912, volume 1.42, section 3, table 23).

d. RESTORE data is shown for the initial procedure for PTCA, angiography and atherectomy, since all subjects underwent angiography ± PTCA/atherectomy (see NDA 20-912, volume 1.55, table 11). CABG data is shown for first 30 days.

**2. Concomitant medications**

All subjects in the three pivotal trials took concomitant cardiac medications. The most common medications: β-blockers, nitrates, calcium-channel blockers, and ASA, were taken by similar percentages of subjects in all three trials. See individual trial summaries for details.

**3. Concomitant heparin use**

Each trial used a slightly different protocol concerning the use of heparin (see appendix 8, section 20 and individual trial designs). Ultimately, the amount and duration of heparin therapy differed in the three trials, as summarized below. No information on the total dose of heparin administered during the PRISM trial is available.

**PRISM-PLUS**

In the PRISM-PLUS trial, heparin was administered to two of the three study arms for the period of study drug administration (up to 106 hours). Any subject who underwent PTCA during the initial infusion period also received another bolus of 27500 U of heparin (open-label).

Table 22.0.1 b.2 (from table 6.2.1.12.1c.3) Dose of heparin administered in the PRISM-PLUS trial<sup>a</sup>.

| Measurement                 | Tirofiban       | Tirofiban +Heparin | Heparin     |
|-----------------------------|-----------------|--------------------|-------------|
| Units of heparin (boluses)  | NA <sup>b</sup> | 6155±7051          | 6439±6801   |
| Units of heparin (infusion) | NA              | 70310±26729        | 70606±27740 |
| Units of heparin (combined) | NA              | 76465±29654        | 77044±30600 |

a. Data from NDA 20-912, volume 1.42, ref. 5, appendix 4.1.6

b. Data for these points not available to the medical reviewer at time of review.

**22.0.1b** Comparability of concomitant therapies received in the PRISM-PLUS, PRISM, and RESTORE trials (cont)

**RESTORE**

Heparin was administered in open-label fashion during the RESTORE trial to both the tirofiban and the placebo arms, during the PTCA. At the conclusion of the procedure, heparin was to be discontinued. As summarized below, the placebo group received more heparin, both measured by total dose and by duration of infusion. The average duration of heparin therapy was 18-20 hours, strongly suggesting that heparin was not discontinued at the end of PTCA as the protocol suggested.

Table 22.0.1b.3 (from table 6.2.3.12.2.1) Heparin dose for subjects in the RESTORE trial”.

|                                        | Tirofiban<br>(n=1071) | Placebo<br>(n=1070) | p value      |
|----------------------------------------|-----------------------|---------------------|--------------|
| <b>Total dose of heparin</b>           |                       |                     |              |
| 0 Units                                | 36 (3.4%)             | 30 (2.8%)           |              |
| 1-4999 Units                           | 19 (1.8%)             | 15 (1.4%)           |              |
| 5000 to 9999 Units                     | 200 (18.8%)           | 188 (17.8%)         |              |
| 10000 to 19999 Units                   | 760 (71.4%)           | 760 (71.8%)         |              |
| >20000 Units                           | 49 (4.6%)             | 65 (6.1%)           |              |
| <b>Mean heparin dose</b>               | <b>10,860.6</b>       | <b>11,376.0</b>     | <b>0.013</b> |
| <b>Duration of Heparin infusion</b>    |                       |                     |              |
| 0 hrs                                  | 300 (28.0%)           | 284 (26.5%)         |              |
| >0 to <6                               | 70 (6.5%)             | 63 (5.9%)           |              |
| 6 to 12 hrs                            | 145 (13.5%)           | 105 (9.9%)          |              |
| > 12 hrs                               | 556 (51.9%)           | 618 (57.8%)         |              |
| <b>Mean duration of infusion (hrs)</b> | <b>18.8</b>           | <b>20.3</b>         | <b>0.035</b> |

Data from NDA volume 1.55, tables 12-13. Shown as n (%).  
p values calculated using t test.

**22.0.1c** Comparability of tirofiban dose in the PRISM-PLUS, PRISM, and RESTORE trials

The duration of tirofiban administration was different in the three studies: up to 108 hours in the PRISM-PLUS trial; 48 hours in the PRISM trial; and 36 hours in the RESTORE trial.

As a result, the total dose of tirofiban administered in each of the studies was also different. As was discussed in section 5.1, subjects in the PRISM and PRISM-PLUS trials, on the average, received more total tirofiban, and received tirofiban for a longer period of time, than did subjects in the RESTORE trial. Subjects in the PRISM-PLUS trial received tirofiban for an average of 72 hours (see table 6.2.1.12.2c.2). Subjects in the PRISM trial received tirofiban for an average of 46 hours (see table 6.2.2.12.2c.2). Subjects in the RESTORE trial received tirofiban for an average of 30 hours (see table 6.2.3.12.2.3).

**22.0.1c Comparability of tirofiban dose in the PRISM-PLUS, PRISM, and RESTORE trials (cont)**

**Comparability of timing of clinical event relative to start of study drug in the three trials**

All three trials enrolled subjects presenting with acute coronary syndrome, but the timing of entry into the trial relative to the clinical event qualifying the subject for entry (i.e., last anginal episode, timing of NQWMI) differed for the PRISM, PRISM-PLUS, and RESTORE trials.

**PRISM-PLUS**

In the PRISM-PLUS trial, subjects were required to have had their last episode of prolonged, repetitive, or postinfarction anginal pain within 12 hours prior to randomization. The timing of entry into the study from last pain to start of study drug is summarized below.

**Table 22.0.1c.1 (from table 6.2.1.12.1.3) Time to administration of study drug after onset of pain in the PRISM-PLUS study<sup>a</sup>**

| <b>Demographic</b>                       | <b>Tirofiban<br/>n=345</b> | <b>Tirofiban +<br/>Heparin<br/>n=773</b> | <b>Heparin<br/>n=797</b> | <b>Total<br/>n=1915</b> |
|------------------------------------------|----------------------------|------------------------------------------|--------------------------|-------------------------|
| <b>Elapsed Time: pain to study start</b> |                            |                                          |                          |                         |
| <3 hours                                 | 38 (11.0%)                 | 113 (14.6%)                              | 119 (15.0%)              | 270 (14.1%)             |
| 3 to 6 hours                             | 102 (29.6%)                | 236 (30.6%)                              | 210 (26.4%)              | 548 (28.7%)             |
| 6 to 12 hours                            | 179 (52.0%)                | 357 (46.2%)                              | 412 (51.8%)              | 948 (49.6%)             |
| 12 to 18 hours                           | 22 (6.4%)                  | 63 (8.2%)                                | 51 (6.4%)                | 136 (7.1%)              |
| 18 to 24 hours                           | 1 (0.3%)                   | 2 (0.3%)                                 | 1 (0.1%)                 | 4 (0.2%)                |
| >24 hours                                | 2 (0.6%)                   | 1 (0.1%)                                 | 3 (0.4%)                 | 6 (0.3%)                |

a. Data from NDA volume 1.42, tables 8. Shown as n (%).

b. Evolving NQWMI was defined as presence of a high-risk anginal presentation without enzyme elevation at randomization, and enzyme evidence of an M.I. within 24 hours of study start without an intercurrent event classified as an endpoint by the Endpoint Committee.

**PRISM**

In the PRISM trial, subjects were required to have had their last episode of prolonged, repetitive, or postinfarction anginal pain within 24 hours prior to randomization. The timing of entry into the study from last pain to start of study drug is summarized below.

**Table 22.0.1c.2 (from table 6.2.2.12.2c.1) Time to administration of study drug after onset of pain in the PRISM study<sup>a</sup>**

| <b>Elapsed time (hrs)</b>                | <b>Tirofiban<br/>n=1616</b> | <b>Heparin<br/>n=1616</b> | <b>Total<br/>n=3232</b> |
|------------------------------------------|-----------------------------|---------------------------|-------------------------|
| <b>Elapsed Time: pain to study start</b> |                             |                           |                         |
| <3 hours                                 | 246 (15.6%)                 | 260 (16.4%)               | 506 (16.0%)             |
| 3 to 6 hours                             | 338 (21.4%)                 | 366 (23.1%)               | 704 (22.3%)             |
| 6 to 12 hours                            | 482 (30.5%)                 | 466 (29.4%)               | 948 (30.0%)             |
| 12 to 18 hours                           | 250 (15.8%)                 | 251 (15.9%)               | 501 (15.8%)             |
| 18 to 24 hours                           | 241 (15.2%)                 | 225 (14.2%)               | 466 (14.7%)             |
| >24 hours                                | 24 (1.5%)                   | 15 (0.9%)                 | 39 (1.2%)               |

a. Data from NDA volume 1.48, ref. 9, table 5.

**RESTORE**

In the RESTORE trial, subjects were required to have undergone PTCA within 72 hours of presentation with unstable angina or acute MI. The time from study event to administration of study drug is summarized below.

**Table 22.0.1c.3 Elapsed time from the entry event to study start in the RESTORE trial<sup>a</sup>**

| <b>Patient Groups</b>     | <b>10th<br/>percentile<br/>(hours)</b> | <b>25th<br/>percentile<br/>(hours)</b> | <b>50th<br/>percentile<br/>(hours)</b> | <b>75th<br/>percentile<br/>(hours)</b> | <b>90th<br/>percentile<br/>(hours)</b> |
|---------------------------|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|
| <b>All patients</b>       | 3.0                                    | 9.6                                    | 26.5                                   | 48.4                                   | 64.8                                   |
| <b>Placebo +heparin</b>   | 3.0                                    | 10.0                                   | 26.8                                   | 49.0                                   | 67.0                                   |
| <b>Tirofiban +heparin</b> | 3.0                                    | 8.9                                    | 26.2                                   | 47.9                                   | 63.6                                   |

a. Data shown is for 202212041 subjects with evaluable data, shown as % of all evaluated subjects.

**22.0.1d Comparability of timing of study drug administration relative to PTCA in the PRISM-PLUS, PRISM, and RESTORE trials**

The three trials differed in the relationship of the timing of study drug infusion to the timing of the PTCA due to differences in protocol design as follows:

1. In PRISM-PLUS, patients were given study drug for at least 48 hours prior to the PTCA, during the PTCA, and up to 12-24 hours following the procedure.
2. In PRISM, angiography and PTCA was deferred until after the completion of study drug infusion. Thus, in this study, patients were given 48 hours of study drug, and there may have been a study drug-free interval between the discontinuation of study drug and the PTCA.
3. In RESTORE, study drug was initiated at the time of PTCA and continued for 36 hours thereafter.

**PRISM-PLUS**

Based on the protocol design of the PRISM-PLUS trial, some subjects underwent PTCA while still receiving study drug. Overall, 58411915 (30.4%) of the subjects underwent PTCA while still receiving study drug. There were 239 in the tirofiban +heparin group (30.9%), 236 in the heparin group (29.6%), and 109 in the tirofiban alone group (3 1.6%). The population that underwent PTCA during study drug administration more closely approximates the RESTORE trial population, which called for PTCA in conjunction with study drug administration.

Because there were a few outlier values for time of PTCA relative to study drug discontinuation, data are presented in the table as the median of distribution of the times along with certain percentiles of the distribution. The table below represents the percentiles of the distribution of the time of PTCA relative to study drug infusion for each of the three groups separately, and for the combined groups. In calculating elapsed times from the end of the study drug infusion to the start of the PTCA, negative times refer to procedures performed while the patient was receiving study drug, and positive times refer to procedures performed after study drug was discontinued. The data suggest that there was a broader range of times when subjects in PRISM-PLUS underwent PTCA, relative to subjects in PRISM (see above).

Table 22.0. Id. 1 Percentiles of distribution for time of PTCA (hrs) relative to study drug discontinuation in subjects who underwent PTCA during the initial hospitalization in the PRISM-PLUS study<sup>a</sup>.

| Patient Groups      | 10th Percentile (hours) | 25th Percentile (hours) | 50th Percentile (hours) | 75th Percentile (hours) | 90th Percentile (hours) |
|---------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| All subjects        | -23.9                   | -19.8                   | -12.1                   | 22.2                    | 118.9                   |
| Tirofiban + Heparin | -23.3                   | -19.4                   | -5.9                    | 28.0                    | 118.9                   |
| Heparin alone       | -23.9                   | -20.4                   | -12.4                   | 0.1                     | 103.3                   |
| Tirofiban alone     | -24.5                   | -19.2                   | -11.7                   | 67.0                    | 188.2                   |

a. The PRISM-PLUS analyses include all subjects with a PTCA during the initial hospitalization. They do not include subjects with a PTCA following a readmission.

**PRISM**

Based on the PRISM protocol, subjects were not undergo cardiac procedures, including PTCA, during the 48 hours of study drug infusion. For this reason, very few subjects (10 total) received study drug during their PTCA (see table below). As shown in the table, 50% of the subjects received their PTCA >66 hours after discontinuing study drug infusion, and <10% of the subjects had their PTCA ≤2 hours after discontinuing study drug infusion.

Table 22.0.1d.2 Percentiles of distribution for time of PTCA (hrs) relative to study drug discontinuation in patients who underwent PTCA in the PRISM study<sup>a</sup>.

| Patient Groups | 10th Percentile (hours) | 25th Percentile (hours) | 50th Percentile (hours) | 75th Percentile (hours) | 90th Percentile (hours) |
|----------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| All patients   | 2.0                     | 21.7                    | 67.5                    | 151.5                   | 310.8                   |
| Heparin        | 1.5                     | 21.3                    | 66.7                    | 144.0                   | 285.6                   |
| Tirofiban      | 3.0                     | 23.1                    | 68.1                    | 161.9                   | 337.8                   |

a. The PRISM analyses include all patients with a PTCA, either during the initial or following a readmission. It was not possible to identify the PTCA procedure as occurring during the initial hospitalization or following a readmission due to the design of the case report forms and the collection of this information in the database. Data from sponsor at request of medical reviewer.

**RESTORE**

Per protocol, all subjects in the RESTORE trial underwent PTCA with or without atherectomy. Also per protocol, all subjects received study drug just prior to and during PTCA.

### 23.0 Appendix Eleven: Bleeding clinical events from the individual phase III trials

The Phase III trials [PRISM-PLUS, PRISM, and RESTORE) contributed the majority of subjects to the overall safety profile of the drug. Each trial, however, had a different design, both in cumulative exposure of subjects to tirofiban and in the concomitant use of invasive cardiac interventions (see individual trial reviews, and appendix 10, p. 370 for discussion). As expected, then, each trial had a unique, design-related bleeding complications profile. Note that, since the findings are related to the respective trials, the comparator groups are the treatment groups **within** the respective trials, not the integrated treatment groups used for the other safety analyses.

Bleeding complications in each respective trial were tabulated from a “Bleeding Complications” case report form, which captured bleeding events reported either as a clinical adverse experience or a laboratory adverse experience on the “Adverse Experience” case report form. Clinically overt bleeding was captured according to the site of the bleeding on the “Bleeding Complications” form; in some cases postoperative bleeding was classified under site “Other” (in particular **after** coronary artery bypass surgery). “Unknown” was used if the patient had a laboratory adverse experience of a decreased **hemoglobin/hematocrit**, but no clinically overt bleeding could be identified by the investigator. **The** laboratory adverse experience of microscopic **hematuria** (“urine red blood cells increased”) was captured on the “Bleeding Complications” form as **GU/Hematuria** “Oozing”; positive fecal occult blood (as a laboratory adverse experience) was captured as GI “Oozing.”

#### 23.1 Bleeding in the PRISM-PLUS Trial

The PRISM-PLUS trial compared the effects of tirofiban alone, tirofiban +**heparin**, and heparin on a variety of clinical cardiac endpoints. The tirofiban alone arm was discontinued due to concerns for excess mortality (discussed in section 8.1.1.1 d above). Because of **this**, and because the sponsor is not seeking an indication for the use of **tirofiban** without concomitant heparin, the **tirofiban** alone group will be reported on, but no comparisons made between it and the other **two** groups.

The first table summarizes the subject discontinuations in the PRISM-PLUS trial. The combination-group had more discontinuations of all types due to **AEs**, and more discontinuations for bleeding **AEs**, when compared **with** the heparin alone group. Twenty-four subjects in the tirofiban +**heparin** group experienced a bleeding AE which led to drug discontinuation, compared with 10 subjects in the heparin group (3.1% vs. **0.9%**, **p=0.002**). These narratives can be found in appendix 4.

Table 23.1.1 Subject discontinuation summary from the PRISM-PLUS trial<sup>a</sup>.

| Clinical event                    | Tirofiban<br>n=345 | Tirofiban<br>+Heparin<br>n=773 | Heparin<br>n=797 | p value T+H<br>vs. H <sup>c</sup> |
|-----------------------------------|--------------------|--------------------------------|------------------|-----------------------------------|
| Discontinued due to an AE         | 9 (2.6%)           | 42 (5.4%)                      | 20 (2.5%)        | 0.004                             |
| Discontinued due to a bleeding AE | 5 (0.4%)           | 24 (3.1%)                      | 7 (0.9%)         | 0.002                             |
| Discontinued due to lab AE        | 2 (0.6%)           | 5 (0.6%)                       | 5 (0.6%)         | 0.99                              |
| Deaths <sup>d</sup>               | 21 (6.1%)          | 30 (3.9%)                      | 39 (4.9%)        | 0.39                              |

a. Data from NDA volume 1.42, ref. 5, table 32, and electronic datasets.

b. Felt to be possibly, probably, or definitely drug-related by individual investigators.

c. p value calculated using chi square test by the sponsor.

d. Counts deaths that occurred prior to closure of the **30-day** safety database, including 5 subjects who died after 30 days.

The next table summarizes the major causes for subject discontinuations in the PRISM-PLUS trial. These were more **frequent** in the tirofiban +**heparin** group (5.4%) than in the heparin group (2.5%, **p=0.004**). This difference was primarily due to increased bleeding **AEs**. A full listing of the discontinuations is found in appendix 4, section 16.0.

23.1 Bleeding in the PRISM-PLUS Trial (cont)

Table 23.1.2 Significant clinical AEs leading to discontinuation in the PRISM-PLUS trial<sup>a</sup>.

|                                          | Tirofiban alone<br>n=345 | Tirofiban + Heparin<br>n=773 | Heparin alone<br>n=797 | p value T+H vs. H <sup>b</sup> |
|------------------------------------------|--------------------------|------------------------------|------------------------|--------------------------------|
| <b>Any Adverse Experience</b>            | 9 (2.6%)                 | 42 (5.4%)                    | 20 (2.5%)              | 0.004                          |
| <b>Body as a Whole/Site Unspecified)</b> | 0 (0%)                   | 0 (0%)                       | 1 (0.1%)               | 0.99                           |
| <b>Cardiovascular System</b>             | 3 (0.9%)                 | 20 (2.6%)                    | 10 (1.3%)              | 0.065                          |
| Bleeding, postoperative                  | 1 (0.3%)                 | 5 (0.6%)                     | 0 (0%)                 | 0.029                          |
| Dissection, coronary artery              | 0 (0%)                   | 5 (0.6%)                     | 0 (0%)                 | 0.029                          |
| Hematoma                                 | 0 (0%)                   | 3 (0.4%)                     | 2 (0.3%)               | 0.68                           |
| <b>Digestive System</b>                  | 3 (0.9%)                 | 6 (0.8%)                     | 2 (0.3%)               | 0.17                           |
| GI hemorrhage                            | 0 (0%)                   | 3 (0.4%)                     | 0 (0%)                 | 0.12                           |
| <b>Hematologic/ Lymphatic</b>            | 1 (0.3%)                 | 6 (0.8%)                     | 1 (0.1%)               | 0.066                          |
| Thrombocytopenia                         | 1 (0.3%)                 | 5 (0.6%)                     | 1 (0.1%)               | 0.12                           |
| <b>Urogenital System</b>                 | 1 (0.3%)                 | 7 (0.9%)                     | 3 (0.4%)               | 0.22                           |

a. Data from NDA vol. 1.42, ref 5, table 35 and electronic datasets.

b. p value calculated using chi square test by the sponsor.

The next table summarizes the discontinuations due to lab abnormalities, showing that there was not significant increase in bleeding-related lab AEs leading to subject withdrawal in the PRISM-PLUS trial.

Table 23.1.3 Laboratory AEs, including AEs leading to discontinuation, in the PRISM-PLUS trial<sup>a</sup>.

|                                              | Tirofiban alone<br>n=345 | Tirofiban + Heparin<br>n=773 | Heparin alone<br>n=797 | p value T+H vs. H <sup>b</sup> |
|----------------------------------------------|--------------------------|------------------------------|------------------------|--------------------------------|
| With any laboratory AE                       | 144 (41.7%)              | 292 (37.8%)                  | 276 (34.6%)            | 0.21                           |
| With drug-related laboratory AE <sup>c</sup> | 83 (24.1%)               | 188 (24.3%)                  | 150 (18.8%)            | 0.008                          |
| With any serious laboratory AE               | 0 (0%)                   | 0 (0%)                       | 3 (0.4%)               | 0.25                           |
| With serious drug-related laboratory AE      | 0 (0%)                   | 0 (0%)                       | 1 (0.1%)               | 0.99                           |
| <b>Discontinued due to a laboratory AE</b>   | 2 (0.6%)                 | 5 (0.6%)                     | 5 (0.6%)               | 0.99                           |
| Discontinued due to bleeding lab AE          | 1 (0.3%)                 | 3 (0.4%)                     | 3 (0.4%)               | 0.99                           |

a. Data from NDA vol. 1.42, ref 5, table 36 and electronic datasets.

b. p value calculated using chi square test by the sponsor

c. Drug-related per individual investigator.

Bleeding AEs in the PRISM-PLUS trial

Per the sponsor, the bleeding in the tirofiban +heparin group was more frequent and ‘somewhat more severe.’ Overall, the combination group experienced oozing 56% and moderate or worse 9.5%, compared with 42.8% and 6.5% respectively for the heparin alone group (p<0.001). This excess bleeding was seen with IV sites, catheterization sites, nosebleeds, GU/hematuria and ‘other’ bleeding sites (primarily post-op bleeding).

Table 23.1.4 Bleeding AEs in the PRISM-PLUS trial<sup>a</sup>.

|                                 | Tirofiban alone<br>n=345 | Tirofiban + Heparin<br>n=773 | Heparin alone<br>n=797 | p value T+H vs. H <sup>b</sup> |
|---------------------------------|--------------------------|------------------------------|------------------------|--------------------------------|
| <b>Any bleeding AE</b>          | 134 (38.8%)              | 340 (44.0%)                  | 456 (57.2%)            | <0.001                         |
| <b>No bleeding complication</b> | 210 (61%)                | 433 (56%)                    | 341 (42.7%)            |                                |

a. Data from NDA vol. 1.42, ref 5, table 40 and electronic datasets.

b. p value calculated using chi square test by the sponsor.

There was no significant difference in the % of subjects who had at least one episode of major bleeding, both by site and as judged by the TIMI classification. Protocol-specified major bleeds occurred in 4% of the combination and 3% of the heparin groups (p=0.34). TIMI-class major bleeds occurred in 1.2% of the combination and 0.8% of the heparin groups (p=0.23).

### 23.1 Bleeding in the PRISM-PLUS Trial (cont)

Table 23.1.5 Major bleeding AEs in the PRISM-PLUS trial<sup>a</sup>.

|                                                      | Tirofiban alone<br>n=345 | Tirofiban + Heparin<br>n=773 | Heparin alone<br>n=797 | p value<br>T+H vs. H <sup>b</sup> |
|------------------------------------------------------|--------------------------|------------------------------|------------------------|-----------------------------------|
| <b>Major Bleeding (protocol defined)<sup>c</sup></b> |                          |                              |                        |                                   |
| No                                                   | 327 (94.8%)              | 742 (96.0%)                  | 773 (97.0%)            | 0.34                              |
| Yes                                                  | 18 (5.2%)                | 31 (4.0%)                    | 24 (3.0%)              |                                   |
| <b>TIMI Bleeding: any</b>                            |                          |                              |                        | 0.077                             |
| Major                                                | 9 (2.6%)                 | 11 (1.4%)                    | 6 (0.8%)               | 0.23                              |
| Minor                                                | 35 (10.1%)               | 81 (10.5%)                   | 64 (8.0%)              | NA                                |
| Loss/ No site identified                             | 2 (0.6%)                 | 5 (0.6%)                     | 7 (0.9%)               | NA                                |

a. Data from NDA vol. 1.42, ref 5, table 40 and electronic datasets.

b. p value calculated using chi square test by the sponsor.

c. Major bleeding defined as bleeding resulting in: hemoglobin drop >5 g/dl; transfusion of 2 units or more; corrective surgery; intracranial hemorrhage; or retroperitoneal hemorrhage.

#### Sites of bleeding in the PRISM-PLUS trial

Compared with the heparin group, there was significantly more overall bleeding, and bleeding for the following sites in the combination group: IVs; catheters; nasal; and GI. The incidence of moderate, severe and life-threatening bleeding are shown below grouped by site of bleeding. Life-threatening bleeds occurred at a similar frequency in the two groups (0.8 vs. 0.6%), and no intracranial or retroperitoneal bleeds occurred in the combination group.

Table 23.1.6 Major bleeding AEs in the PRISM-PLUS trial<sup>a</sup>.

|                      | Tirofiban alone<br>n=345 | Tirofiban + Heparin<br>n=773 | Heparin alone<br>n=797 | p-value<br>(T+H vs. H) <sup>b</sup> |
|----------------------|--------------------------|------------------------------|------------------------|-------------------------------------|
| <b>Any site</b>      |                          |                              |                        | <0.001                              |
| Oozing               | 75 (21.7%)               | 171 (22.1%)                  | 149 (18.7%)            |                                     |
| Mild                 | 97 (28.1%)               | 188 (24.3%)                  | 139 (17.4%)            |                                     |
| Moderate             | 24 (7.0%)                | 50 (6.5%)                    | 36 (4.5%)              |                                     |
| Severe               | 6 (1.6%)                 | 17 (2.2%)                    | 11 (1.4%)              |                                     |
| Life-threatening     | 8 (2.3%)                 | 6 (0.8%)                     | 5 (0.6%)               |                                     |
| <b>IV site</b>       |                          |                              |                        | 0.049                               |
| Oozing               | 24 (7.0%)                | 59 (7.6%)                    | 47 (5.9%)              |                                     |
| Mild                 | 14 (4.1%)                | 36 (4.7%)                    | 31 (3.9%)              |                                     |
| Moderate             | 1 (0.3%)                 | 7 (0.9%)                     | 2 (0.3%)               |                                     |
| Severe               | 0 (0%)                   | 0 (0%)                       | 0 (0%)                 |                                     |
| Life-threatening     | 0 (0%)                   | 0 (0%)                       | 0 (0%)                 |                                     |
| <b>Catheter site</b> |                          |                              |                        | 0.016                               |
| Oozing               | 56 (16.2%)               | 102 (13.2%)                  | 82 (10.3%)             |                                     |
| Mild                 | 45 (13.0%)               | 70 (9.1%)                    | 60 (7.5%)              |                                     |
| Moderate             | 17 (4.9%)                | 14 (1.9%)                    | 14 (1.8%)              |                                     |
| Severe               | 2 (0.6%)                 | 7 (0.9%)                     | 3 (0.4%)               |                                     |
| Life-threatening     | 2 (0.6%)                 | 0 (0%)                       | 0 (0%)                 |                                     |
| <b>Oral</b>          |                          |                              |                        | 0.096                               |
| Oozing               | 3 (0.9%)                 | 3 (0.4%)                     | 2 (0.3%)               |                                     |
| Mild                 | 3 (0.9%)                 | 6 (0.8%)                     | 0 (0%)                 |                                     |
| Moderate             | 0 (0%)                   | 1 (0.1%)                     | 2 (0.3%)               |                                     |
| Severe               | 0 (0%)                   | 0 (0%)                       | 0 (0%)                 |                                     |
| Life-threatening     | 0 (0%)                   | 0 (0%)                       | 0 (0%)                 |                                     |
| <b>Nasal</b>         |                          |                              |                        | <0.001                              |
| Oozing               | 25 (7.2%)                | 28 (3.6%)                    | 13 (1.6%)              |                                     |
| Mild                 | 18 (5.2%)                | 31 (4.0%)                    | 3 (0.4%)               |                                     |
| Moderate             | 1 (0.3%)                 | 2 (0.3%)                     | 0 (0%)                 |                                     |
| Severe               | 0 (0%)                   | 0 (0%)                       | 0 (0%)                 |                                     |
| Life-threatening     | 0 (0%)                   | 0 (0%)                       | 0 (0%)                 |                                     |

23.1 Bleeding in the PRISM-PLUS Trial (cont)

Table 23.1.7 Major bleeding AEs in the PRISM-PLUS trial (cont)<sup>a</sup>.

|                        | Tirofiban alone<br>n=345 | Tirofiban + Heparin<br>n=773 | Heparin alone<br>n=797 | p-value<br>(T+H vs. H) <sup>b</sup> |
|------------------------|--------------------------|------------------------------|------------------------|-------------------------------------|
| <b>GU/ Hematuria</b>   |                          |                              |                        | <0.001                              |
| Oozing                 | 23 (6.7%)                | 59 (7.6%)                    | 47 (5.9%)              |                                     |
| Mild                   | 32 (9.3%)                | 69 (8.9%)                    | 42 (5.3%)              |                                     |
| Moderate               | 3 (0.9%)                 | 10 (1.3%)                    | 6 (0.8%)               |                                     |
| Severe                 | 0 (0%)                   | 2 (0.3%)                     | 1 (0.1%)               |                                     |
| Life-threatening       | 0 (0%)                   | 0 (0%)                       | 0 (0%)                 |                                     |
| <b>GI</b>              |                          |                              |                        | <0.001                              |
| Oozing                 | 21 (6.1%)                | 42 (5.4%)                    | 27 (3.4%)              |                                     |
| Mild                   | 15 (4.3%)                | 33 (4.3%)                    | 20 (2.5%)              |                                     |
| Moderate               | 3 (0.9%)                 | 10 (1.3%)                    | 2 (0.3%)               |                                     |
| Severe                 | 0 (0%)                   | 2 (0.3%)                     | 0 (0%)                 |                                     |
| Life-threatening       | 2 (0.6%)                 | 2 (0.3%)                     | 0 (0%)                 |                                     |
| <b>Hemoptysis</b>      |                          |                              |                        | 0.15                                |
| Oozing                 | 3 (0.9%)                 | 6 (0.8%)                     | 3 (0.4%)               |                                     |
| Mild                   | 2 (0.6%)                 | 3 (0.4%)                     | 1 (0.1%)               |                                     |
| Moderate               | 0 (0%)                   | 0 (0%)                       | 0 (0%)                 |                                     |
| Severe                 | 0 (0%)                   | 0 (0%)                       | 0 (0%)                 |                                     |
| Life-threatening       | 0 (0%)                   | 0 (0%)                       | 0 (0%)                 |                                     |
| <b>Intracranial</b>    |                          |                              |                        | NA <sup>b</sup>                     |
| Oozing                 | 0 (0%)                   | 0 (0%)                       | 0 (0%)                 |                                     |
| Mild                   | 0 (0%)                   | 0 (0%)                       | 0 (0%)                 |                                     |
| Moderate               | 0 (0%)                   | 0 (0%)                       | 0 (0%)                 |                                     |
| Severe                 | 0 (0%)                   | 0 (0%)                       | 0 (0%)                 |                                     |
| Life-threatening       | 0 (0%)                   | 0 (0%)                       | 0 (0%)                 |                                     |
| <b>Retroperitoneal</b> |                          |                              |                        | 0.33                                |
| Oozing                 | 0 (0%)                   | 0 (0%)                       | 0 (0%)                 |                                     |
| Mild                   | 0 (0%)                   | 0 (0%)                       | 0 (0%)                 |                                     |
| Moderate               | 1 (0.3%)                 | 0 (0%)                       | 0 (0%)                 |                                     |
| Severe                 | 1 (0.3%)                 | 0 (0%)                       | 0 (0%)                 |                                     |
| Life-threatening       | 0 (0%)                   | 0 (0%)                       | 1 (0.1%)               |                                     |
| <b>Other</b>           |                          |                              |                        | 0.009                               |
| Oozing                 | 11 (3.2%)                | 21 (2.7%)                    | 8 (1.0%)               |                                     |
| Mild                   | 9 (2.6%)                 | 16 (2.1%)                    | 8 (0.1%)               |                                     |
| Moderate               | 2 (0.6%)                 | 8 (1.0%)                     | 10 (1.3%)              |                                     |
| Severe                 | 3 (0.9%)                 | 5 (0.6%)                     | 3 (0.4%)               |                                     |
| Life-threatening       | 4 (1.2%)                 | 4 (0.5%)                     | 3 (0.4%)               |                                     |

<sup>a</sup>Data from NDA vol. 1.42, ref 5, table 40 and electronic datasets. Definitions of categories can be found in section 8.1.5.3  
<sup>b</sup>p value calculated using chi square test by the sponsor. NA, no statistical analysis due to small subject numbers.

**Transfusion in PRISM-PLUS**

More subjects in the combination group (4.0%) than in the heparin group (2.8%) required a transfusion, although this difference was not statistically significant (p=0.21). Twenty-seven (3.5%) subjects in the combination group and 18 (2.3%) subjects in the heparin group received transfusions of packed red blood cells (p=0.17). Five (0.6%) of the subjects in the combination group received platelet transfusions compared to 4 (0.5%) of the subjects in the heparin group (p=0.75). In the subjects who did receive platelet transfusions, there were no differences in the number of transfused units between the two treatment groups.

23.1 Bleeding in the PRISM-PLUS Trial

Table 23.1.8 Subjects requiring transfusion in the PRISM-PLUS trial<sup>a</sup>.

|                         | Tirofiban<br>(N=345) | Comb.<br>(N=773) | Heparin<br>(N=797) | p value<br>T+H vs. H |
|-------------------------|----------------------|------------------|--------------------|----------------------|
| <b>Type</b>             | n (%)                | n (%)            | n (%)              |                      |
| <b>Any Transfusion</b>  |                      |                  |                    | 0.21                 |
| No                      | 327 (94.8%)          | 742 (96.0%)      | 775 (97.2%)        |                      |
| Yes                     | 18 (5.2%)            | 31 (4.0%)        | 22 (2.8%)          |                      |
| <b>Whole Blood</b>      |                      |                  |                    | 0.72                 |
| No                      | 343 (99.4%)          | 769 (99.5%)      | 794 (99.6%)        |                      |
| Yes                     | 2 (0.6%)             | 4 (0.5%)         | 3 (0.4%)           |                      |
| <b>FFP</b>              |                      |                  |                    | 0.79                 |
| No                      | 339 (98.3%)          | 766 (99.1%)      | 791 (99.2%)        |                      |
| Yes                     | 6 (1.7%)             | 7 (0.9%)         | 6 (0.8%)           |                      |
| <b>PRBC</b>             |                      |                  |                    | 0.17                 |
| No                      | 328 (95.1%)          | 746 (96.5%)      | 779 (97.7%)        |                      |
| Yes                     | 17 (4.9%)            | 27 (3.5%)        | 18 (2.3%)          |                      |
| <b>Cryoprecipitates</b> |                      |                  |                    | 0.99                 |
| No                      | 345 (100%)           | 772 (99.9%)      | 796 (99.9%)        |                      |
| Yes                     | 0 (0.0%)             | 1 (0.1%)         | 1 (0.1%)           |                      |
| <b>Platelets</b>        |                      |                  |                    | 0.75                 |
| No                      | 342 (99.1%)          | 768 (99.4%)      | 793 (99.5%)        |                      |
| Yes                     | 3 (0.9%)             | 5 (0.6%)         | 4 (0.5%)           |                      |
| <b>Other</b>            |                      |                  |                    | 0.68                 |
| No                      | 345 (100%)           | 770 (99.6%)      | 795 (99.7%)        |                      |
| Yes                     | 0 (0.0%)             | 3 (0.4%)         | 2 (0.3%)           |                      |

a. Data from sponsor at request of medical reviewer.

Table 23.1.9 Number of PRBC units transfused in the PRISM-PLUS trial<sup>a</sup>.

|                            | Tirofiban<br>(N=345) | Comb.<br>(N=773) | Heparin<br>(N=797) | p value<br>T+H vs. H |
|----------------------------|----------------------|------------------|--------------------|----------------------|
| <b>Type and # of Units</b> | n (%)                | n (%)            | n (%)              |                      |
| <b>Whole Blood</b>         |                      |                  |                    |                      |
| 0                          | 343 (99.4%)          | 769 (99.5%)      | 794 (99.6%)        |                      |
| 1                          | 1 (0.3%)             | 2 (0.3%)         | 1 (0.1%)           |                      |
| 2                          | 1 (0.3%)             | 1 (0.1%)         | 2 (0.2%)           |                      |
| 4                          | 0 (0.0%)             | 1 (0.1%)         | 0 (0.0%)           |                      |
| Mean (+S.D.)               | .009 (.120)          | .010 (0.169)     | .006 (.106)        | 0.87                 |
| <b>FFP</b>                 |                      |                  |                    |                      |
| 0                          | 339 (98.3%)          | 766 (99.1%)      | 791 (99.2%)        |                      |
| 1                          | 1 (0.3%)             | 0 (0.0%)         | 1 (0.1%)           |                      |
| 2                          | 2 (0.6%)             | 2 (0.3%)         | 3 (0.4%)           |                      |
| 3                          | 0 (0.0%)             | 1 (0.1%)         | 0 (0.0%)           |                      |
| 4 or more                  | 3 (0.8%)             | 4 (0.5%)         | 2 (0.3%)           |                      |
| Mean (+S.D.)               | .052 (.435)          | .045 (.575)      | .020 (.260)        | 0.29                 |
| <b>PRBC</b>                |                      |                  |                    |                      |
| 0                          | 328 (95.1%)          | 746 (96.5%)      | 779 (97.7%)        |                      |
| 1                          | 0 (0.0%)             | 5 (0.6%)         | 3 (0.4%)           |                      |
| 2                          | 8 (2.3%)             | 14 (1.8%)        | 7 (0.9%)           |                      |
| 3                          | 0 (0.0%)             | 1 (0.1%)         | 2 (0.2%)           |                      |
| 4 or more                  | 9 (2.6%)             | 7 (1.0%)         | 6 (0.8%)           |                      |
| Mean (+S.D.)               | .194 (.988)          | .106 (.732)      | .077 (.628)        | 0.054                |
| <b>Platelets</b>           |                      |                  |                    |                      |
| 0                          | 342 (99.1%)          | 768 (99.4%)      | 793 (99.5%)        |                      |
| 1                          | 0 (0.0%)             | 0 (0.0%)         | 1 (0.1%)           |                      |
| 6                          | 1 (0.3%)             | 0 (0.0%)         | 0 (0.0%)           |                      |
| 8                          | 0 (0.0%)             | 3 (0.4%)         | 1 (0.1%)           |                      |
| 9 or more                  | 2 (0.6%)             | 2 (0.2%)         | 2 (0.3%)           |                      |
| Mean (+S.D.)               | .128 (1.48)          | .067 (.873)      | .035 (.555)        | 0.76                 |

a. Data from sponsor at request of medical reviewer

## 23.2 Bleeding in the PRISM Trial

### Discontinuations for bleeding in the PRISM trial

As shown below, more subjects in the tirofiban +heparin group were discontinued for bleeding AEs. The next table summarizes the major causes for subject discontinuations in the PRISM-PLUS trial. These were more frequent in the tirofiban +heparin group (5.4%) than in the heparin group (2.5%,  $p=0.004$ ). This difference was primarily due to increased bleeding AEs. A full listing of the discontinuations is found in appendix 4, section 16.0.

Table 23.2.1 Subject discontinuation summary from the PRISM trial<sup>a</sup>.

| Clinical event                    | Tirofiban<br>n=1616 | Heparin<br>n=1616 | p value |
|-----------------------------------|---------------------|-------------------|---------|
| Discontinued due to an AE         | 36 (2.2%)           | 19 (1.2%)         | 0.029   |
| Discontinued due to a bleeding AE | 17 (1.1%)           | 6 (0.4%)          | 0.034   |
| Discontinued due to lab AE        | 8 (0.5%)            | 5 (0.3%)          | 0.58    |
| Deaths <sup>d</sup>               | 40 (2.5%)           | 62 (3.8%)         | 0.034   |

a. Data from NDA volume 1.42, ref. 5, table 32, and electronic datasets.

b. Felt to be possibly, probably, or definitely drug-related by individual investigators.

c. p value calculated using chi square analysis.

d. Counts **deaths** that occurred prior to closure of the 30day safety database, including 6 subjects who died after 30 days (3 in each treatment group).

As shown above, more subjects in the tirofiban group were discontinued for bleeding AEs. The next table summarizes the major causes for subject discontinuations in the PRISM trial.

Table 23.2.2 Clinical bleeding AEs leading to discontinuation in the PRISM trial

|                                                          | Tirofiban<br>alone<br>n=1616 | Heparin<br>alone<br>n=1616 | p value <sup>b</sup> |
|----------------------------------------------------------|------------------------------|----------------------------|----------------------|
| Any Adverse Experience<br>(resulting in discontinuation) | 36 (2.2%)                    | 19 (1.2%)                  | 0.029                |
| Body as a Whole/Site Unspecified)                        | 4 (0.2%)                     | 2 (0.1%)                   | 0.69                 |
| Cardiovascular System                                    | 7 (0.4%)                     | 5 (0.3%)                   | 0.77                 |
| Digestive System                                         | 11 (0.7%)                    | 3 (0.2%)                   |                      |
| Fecal occult blood                                       | 1 (0.1%)                     | 0 (0%)                     | 0.99                 |
| Hemorrhage, anal/rectal                                  | 2 (0.1%)                     | 0 (0%)                     | 0.50                 |
| Hemorrhage, gastrointestinal                             | 2 (0.1%)                     | 0 (0%)                     | 0.50                 |
| Hemorrhage, GI-lower                                     | 1 (0.1%)                     | 0 (0%)                     | 0.99                 |
| Melena                                                   | 2 (0.1%)                     | 0 (0%)                     | 0.50                 |
| Ulcer, gastric, with hemorrhage                          | 0 (0%)                       | 1 (0.1%)                   | 0.99                 |
| <b>Hematologic/ Lymphatic</b>                            | 6 (0.4%)                     | 0 (0%)                     | 0.031                |
| <b>Petechiae</b>                                         | 1 (0.1%)                     | 0 (0%)                     | 0.99                 |
| Thrombocytopenia                                         | 5 (0.3%)                     | 0 (0%)                     | 0.062                |
| Nervous system                                           | 1 (0.1%)                     | 4 (0.2%)                   | 0.38                 |
| Confusion                                                | 0 (0%)                       | 3 (0.2%)                   | 0.25                 |
| Respiratory system                                       | 3 (0.2%)                     | 2 (0.1%)                   | 0.99                 |
| Epistaxis                                                | 2 (0.1%)                     | 1 (0.1%)                   | 0.99                 |
| Hemoptysis                                               | 1 (0.1%)                     | 0 (0.1%)                   | 0.99                 |
| Urogenital system                                        | 3 (0.2%)                     | 3 (0.2%)                   | 0.99                 |
| Dysfunctional uterine bleeding                           | 1 (0.1%)                     | 0 (0%)                     | 0.99                 |
| Hematuria                                                | 2 (0.1%)                     | 3 (0.2%)                   | 0.99                 |

a. Data from NDA volume 1.48, reference 9, tables 35.

b. p value calculated using chi square test.

The sponsor also collected the laboratory AEs during the trial, including those leading to discontinuation. As summarized below, more subjects in the tirofiban group had a laboratory AE and had a drug-related lab AE than the subjects in the heparin group. This increase was primarily due to increased incidence of two labs in the tirofiban group: thrombocytopenia (2.0% vs. 0.9% in the heparin group,  $n=0.013$ ); and increased hematuria (8.7% vs. 6.2% in the heparin group,  $p=0.008$ ).

## 23.2 Bleeding in the PRISM Trial

Table 23.2.3 Laboratory AEs, including AEs leading to discontinuation, in the PRISM trial<sup>a</sup>.

|                                              | Tirofiban<br>alone<br>n=345 | Heparin<br>alone<br>n=797 | p value <sup>b</sup> |
|----------------------------------------------|-----------------------------|---------------------------|----------------------|
| With any laboratory AE                       | 346 (21.4%)                 | 297 (18.4%)               | 0.034                |
| With drug-related laboratory AE <sup>c</sup> | 79 (4.9%)                   | 41 (2.5%)                 | 0.001                |
| With any serious laboratory AE               | 8 (0.5%)                    | 4 (0.2%)                  | 0.39                 |
| With serious drug-related laboratory AE      | 4 (0.2%)                    | 0 (0%)                    | 0.12                 |
| Discontinued due to a laboratory AE          | 8 (0.5%)                    | 5 (0.3%)                  | 0.58                 |
| Discontinued due to bleeding lab AE          | 1 (0.1%)                    | 4 (0.2%)                  | 0.37                 |

a. Data from NDA volume 1.48, reference 9, tables 36.

b. p value calculated using chi square test.

c. Drug-related per individual investigator.

### Bleeding AEs in the PRISM trial

Per the sponsor, the bleeding was 'considerably more frequent in the tirofiban group.'

There was no significant difference in the % of subjects who had at least one episode of major bleeding, both by site and as judged by the TIMI classification. Protocol-specified major bleeds occurred in 21 (1.3%)% of the tirofiban and 14 (0.9%) of the heparin groups (p=0.31). TIMI-class major bleeds occurred in 0.4% of the tirofiban and 0.4% of the heparin groups (p=0.91).

Table 23.2.4 Major bleeding AEs in the PRISM trial<sup>a</sup>.

|                                                | Tirofiban<br>n=1616 | Heparin<br>n=1616 | p value<br>T vs. H <sup>b</sup> |
|------------------------------------------------|---------------------|-------------------|---------------------------------|
| Major Bleeding (protocol defined) <sup>c</sup> |                     |                   |                                 |
| Yes                                            | 21 (1.3%)           | 14 (0.9%)         | 0.31                            |
| TIMI Bleeding                                  |                     |                   | 0.91                            |
| Major                                          | 7 (0.4%)            | 6 (0.4%)          |                                 |
| Minor                                          | 33 (2.0%)           | 31 (1.9%)         |                                 |
| Loss/ No site identified                       | 3 (0.2%)            | 4 (0.2%)          |                                 |

a. Data from NDA vol. 1.48, ref 9, table 40 and electronic datasets.

b. p value calculated using chi square test

c. Major bleeding defined as bleeding resulting in: hemoglobin drop >5 g/dl; transfusion of 2 units or more; corrective surgery; intracranial hemorrhage; or retroperitoneal hemorrhage.

### Sites of bleeding in the PRISM trial

The incidence of moderate, severe and life-threatening bleeding are shown below grouped by site of bleeding. There was a significant increase in the incidence of bleeding in the tirofiban group at the following sites: oral; nasal; GU; GI; pulmonary (**hemoptysis**); other; and unknown. Life-threatening bleeds occurred at a similar frequency in the two groups (0.6 vs. 0.4%). Note, however, the increased frequency of moderate, severe, and life-threatening bleeding the GI category for the tirofiban group.

Two subjects in both groups (0.1%) had intracranial bleeds, and one subject in the tirofiban group had a life-threatening retroperitoneal bleed. Classified under the 'other' category were two episodes of pericardial/mediastinal bleeding in the tirofiban group (AN 2545, and 5597), and one in the heparin group (AN 2467).

23.2 Bleeding in the PRISM Trial

Table 23.2.5 Bleeding AEs grouped according to site in the PRISM trial<sup>†</sup>.

|                      | Tirofiban<br>n=1616 | Heparin<br>n=1616 | p-value |
|----------------------|---------------------|-------------------|---------|
| <b>Any site</b>      |                     |                   | <0.001  |
| Oozing               | 205 (12.7%)         | 134 (8.3%)        |         |
| Mild                 | 151 (9.3%)          | 98 (6.1%)         |         |
| Moderate             | 33 (2.0%)           | 27 (1.7%)         |         |
| Severe               | 17 (1.1%)           | 13 (0.8%)         |         |
| Life-threatening     | 10 (0.6%)           | 7 (0.4%)          |         |
| <b>IV site</b>       |                     |                   | 0.048   |
| Oozing               | 41 (2.5%)           | 25 (1.5%)         |         |
| Mild                 | 25 (1.5%)           | 18 (1.1%)         |         |
| Moderate             | 2 (0.1%)            | 3 (0.2%)          |         |
| Severe               | 0 (0%)              | 0 (0%)            |         |
| Life-threatening     | 0 (0%)              | 1 (0.1%)          |         |
| <b>Catheter site</b> |                     |                   | 0.71    |
| Oozing               | 16 (1.0%)           | 16 (1.0%)         |         |
| Mild                 | 7 (0.4%)            | 9 (0.6%)          |         |
| Moderate             | 5 (0.3%)            | 6 (0.4%)          |         |
| Severe               | 4 (0.2%)            | 3 (0.2%)          |         |
| Life-threatening     | 0 (0%)              | 1 (0.1%)          |         |
| <b>Oral</b>          |                     |                   | 0.018   |
| Oozing               | 9 (0.6%)            | 1 (0.1%)          |         |
| Mild                 | 4 (0.2%)            | 2 (0.1%)          |         |
| Moderate             | 1 (0.1%)            | 1 (0.1%)          |         |
| Severe               | 0 (0%)              | 0 (0%)            |         |
| Life-threatening     | 0 (0%)              | 0 (0%)            |         |
| <b>Nasal</b>         |                     |                   | co.00 1 |
| Oozing               | 48 (5.3%)           | 10 (0.6%)         |         |
| Mild                 | 33 (3.9%)           | 5 (0.3%)          |         |
| Moderate             | 2 (0.1%)            | 1 (0.1%)          |         |
| Severe               | 0 (0%)              | 0 (0%)            |         |
| Life-threatening     | 0 (0%)              | 0 (0%)            |         |
| <b>GU/ Hematuria</b> |                     |                   | 0.004   |
| Oozing               | 84 (9.3%)           | 65 (4.0%)         |         |
| Mild                 | 63 (5.3%)           | 38 (2.4%)         |         |
| Moderate             | 7 (0.4%)            | 7 (0.4%)          |         |
| Severe               | 1 (0.1%)            | 1 (0.1%)          |         |
| Life-threatening     | 0 (0%)              | 0 (0%)            |         |
| <b>GI</b>            |                     |                   | 0.002   |
| Oozing               | 36 (2.2%)           | 27 (1.7%)         |         |
| Mild                 | 28 (1.7%)           | 14 (0.9%)         |         |
| Moderate             | 9 (0.6%)            | 3 (0.2%)          |         |
| Severe               | 5 (0.3%)            | 3 (0.2%)          |         |
| Life-threatening     | 3 (0.2%)            | 0 (0%)            |         |
| <b>Hemoptysis</b>    |                     |                   | 0.032   |
| Oozing               | 4 (0.2%)            | 1 (0.1%)          |         |
| Mild                 | 6 (0.4%)            | 2 (0.2%)          |         |
| Moderate             | 1 (0.1%)            | 0 (0%)            |         |
| Severe               | 0 (0%)              | 0 (0%)            |         |
| Life-threatening     | 0 (0%)              | 0 (0%)            |         |

## 23.2 Bleeding in the PRISM Trial

Table 23.2.5 Bleeding AEs, grouped according to site in the PRISM trial (cont)

|                        | Tirofiban<br>n=1616 | Heparin<br>n=1616 | p-value |
|------------------------|---------------------|-------------------|---------|
| <b>Intracranial</b>    |                     |                   | 0.99    |
| Oozing                 | 1 (0.1%)            | 0 (0%)            |         |
| Mild                   | 1 (0.1%)            | 0 (0%)            |         |
| Moderate               | 0 (0%)              | 0 (0%)            |         |
| Severe                 | 0 (0%)              | 0 (0%)            |         |
| Life-threatening       | 0 (0%)              | 2 (0.1%)          |         |
| <b>Retroperitoneal</b> |                     |                   | 0.99    |
| Oozing                 | 0 (0%)              | 0 (0%)            |         |
| Mild                   | 0 (0%)              | 0 (0%)            |         |
| Moderate               | 0 (0%)              | 1 (0.1%)          |         |
| Severe                 | 0 (0%)              | 0 (0%)            |         |
| Life-threatening       | 1 (0.1%)            | 0 (0%)            |         |
| <b>Other</b>           |                     |                   | 0.011   |
| Oozing                 | 15 (0.9%)           | 5 (0.3%)          |         |
| Mild                   | 8 (0.5%)            | 4 (0.2%)          |         |
| Moderate               | 4 (0.2%)            | 4 (0.2%)          |         |
| Severe                 | 5 (0.3%)            | 2 (0.1%)          |         |
| Life-threatening       | 6 (0.4%)            | 4 (0.2%)          |         |

Data from NDA vol. 1.48, rcf 9, table 43.

p value calculated using chi square test by the sponsor.

**Transfusion in the PRISM trial** More subjects in the tirofiban group (2.4%) than in the heparin group (1.4%) required a transfusion, although this difference was not statistically significant ( $p=0.070$ ). Similarly, subjects in the tirofiban group required on average more units of packed red blood cells (0.066) than subjects in the heparin group (0.056), a difference that was also not statistically significant ( $p=0.12$ ).

Table 23.2.6 Percent of subjects requiring transfusions in the PRISM trial.

|                         | Tirofiban<br>(N=1616) | Heparin<br>(N=1616) | p value<br>T vs. H |
|-------------------------|-----------------------|---------------------|--------------------|
| <b>Type</b>             | n                     | n                   | p-value            |
| <b>Any Transfusion</b>  |                       |                     | 0.070              |
| No                      | 1578 (97.6%)          | 1593 (98.6%)        |                    |
| Yes                     | 38 (2.4%)             | 23 (1.4%)           |                    |
| <b>Whole Blood</b>      |                       |                     | 0.69               |
| No                      | 1612 (99.8%)          | 1614 (99.9%)        |                    |
| Yes                     | 4 (0.2%)              | 2 (0.1%)            |                    |
| <b>FFP</b>              |                       |                     | 0.55               |
| No                      | 1609 (99.6%)          | 1612 (99.8%)        |                    |
| Yes                     | 7 (0.4%)              | 4 (0.2%)            |                    |
| <b>PRBC</b>             |                       |                     | 0.16               |
| No                      | 1585 (98.1%)          | 1596 (98.8%)        |                    |
| Yes                     | 31 (1.9%)             | 20 (1.2%)           |                    |
| <b>Cryoprecipitates</b> |                       |                     | 0.99               |
| No                      | 1615 (99.9%)          | 1616 (100%)         |                    |
| Yes                     | 1 (0.1%)              | 0 (0.0%)            |                    |
| <b>Platelets</b>        |                       |                     | 0.18               |
| No                      | 1606 (99.4%)          | 1612 (99.8%)        |                    |
| Yes                     | 10 (0.6%)             | 4 (0.2%)            |                    |
| <b>Other</b>            |                       |                     | 0.62               |
| No                      | 1613 (99.8%)          | 1615 (99.9%)        |                    |
| Yes                     | 3 (0.2%)              | 1 (0.1%)            |                    |

a. Data from sponsor at request of medical reviewer.

### 23.2 Bleeding in the PRISM Trial

Tab 23.2.7 Number of PRBC units transfused per subject in the PRISM trial<sup>a</sup>.

| Type and # of transfusions | Tirofiban (N=1616) | Heparin (N=1616) | p-value |
|----------------------------|--------------------|------------------|---------|
| Whole Blood                | n                  | n                |         |
| 0                          | 1612 (99.8%)       | 1614 (99.9%)     |         |
| 1                          | 1 (0.1%)           | 1 (0.1%)         |         |
| 2                          | 1 (0.1%)           | 1 (0.1%)         |         |
| 3                          | 1 (0.1%)           | 0 (0.0%)         |         |
| 4 or more                  | 1 (0.1%)           | 0 (0.1%)         |         |
| Mean (sd)                  | .006 (.136)        | .002 (.056)      | 0.41    |
| FFP                        |                    |                  |         |
| 0                          | 1609 (99.6%)       | 1612 (99.8%)     |         |
| 1                          | 1 (0.1%)           | 0 (0.0%)         |         |
| 2                          | 2 (0.1%)           | 1 (0.1%)         |         |
| 3                          | 2 (0.1%)           | 1 (0.1%)         |         |
| 4 or more                  | 4 (0.2%)           | 3 (0.2%)         |         |
| Mean (sd)                  | .015 (.273)        | .021 (.504)      | 0.37    |
| PRBC                       |                    |                  |         |
| 0                          | 1585 (98.1%)       | 1596 (98.8%)     |         |
| 1                          | 6 (0.4%)           | 1 (0.1%)         |         |
| 2                          | 11 (0.7%)          | 10 (0.6%)        |         |
| 3                          | 4 (0.2%)           | 3 (0.2%)         |         |
| 4 or more                  | 10 (0.6%)          | 6 (0.4%)         |         |
| Mean (sd)                  | .066 (.648)        | .056 (.084)      | 0.12    |
| Platelets                  |                    |                  |         |
| 0                          | 1606 (99.4%)       | 1612 (99.8%)     |         |
| 1                          | 1 (0.1%)           | 1 (0.1%)         |         |
| 2                          | 1 (0.1%)           | 0 (0.0%)         |         |
| 3                          | 1 (0.1%)           | 0 (0.0%)         |         |
| 4 or more                  | 7 (0.4%)           | 3 (0.2%)         |         |
| Mean (sd)                  | .031 (.431)        | .028 (.713)      | 0.11    |

<sup>a</sup> Data from sponsor at request of medical reviewer.

### 23.3 Bleeding in the RESTORE Trial

In the RESTORE trial, subjects received tirofiban or placebo in addition to a regimen of heparin and ASA. All subjects underwent angioplasty as part of the inclusion criteria.

#### Subject discontinuation due to bleeding AEs in the RESTORE trial

More subject in the tirofiban +heparin group discontinued due to bleeding AEs than in the placebo +heparin group. The next table shows the incidence of clinical AEs leading to subject discontinuation. Significantly more subjects in the tirofiban group were discontinued for bleeding AEs. A list of all subject discontinuations for the RESTORE trial appears in section 16.0 (appendix 4).

Table 23.3.1 Reasons for subject discontinuation in the RESTORE trial<sup>a</sup>.

|                                              | Tirofiban<br>n=1071 | Placebo<br>n=1070 | p value <sup>b</sup> |
|----------------------------------------------|---------------------|-------------------|----------------------|
| <b>Discontinued due to an AE<sup>c</sup></b> | 109 (10.2%)         | 91 (8.5%)         |                      |
| <b>Bleeding AE</b>                           | 41 (3.8%)           | 13 (1.2%)         | <0.001               |
| <b>Non-bleeding AE</b>                       | 24 (2.2%)           | 21 (2.0%)         | 0.655                |
| <b>Stent usage</b>                           | 60 (5.6%)           | 76 (7.1%)         | 0.152                |

a. Data from NDA vol. 1.55, ref 11, table 30, and 1.47, ref. 7, table 25.

b. p value calculated using chi square test.

The clinical AEs and laboratory AEs that resulted in discontinuation in the RESTORE trial are summarized in the two tables below, for all AEs occurring  $\geq 0.5\%$  of either treatment group. Note the significant increase in post-operative bleeding in the tirofiban group relative to placebo. The increased number of discontinuations in the Digestive System for tirofiban comes from GI bleeding, discussed in section 8.1 and 8.2. The bleeding discontinuations will be discussed below. Laboratory AEs related to bleeding were more common in the tirofiban group.

Table 23.3.2 Clinical AEs, including bleeding AEs, leading to discontinuation in the RESTORE trial<sup>a</sup>.

|                                            | Tirofiban<br>n=1071 | Placebo<br>n=1070 | p value <sup>b</sup> |
|--------------------------------------------|---------------------|-------------------|----------------------|
| <b>Any Adverse Experience</b>              | 109 (10.2%)         | 91 (8.5%)         | 0.160                |
| <b>Body as a Whole/Site Unspecified)</b>   | 5 (0.5%)            | 4 (0.4%)          | 1.000                |
| <b>Cardiovascular System</b>               | 85 (7.9%)           | 77 (7.2%)         | 0.567                |
| Bleeding, postoperative                    | 22 (2.0%)           | 6 (0.5%)          | 0.004                |
| Dissection, coronary artery                | 42 (3.9%)           | 52 (4.9%)         | 0.294                |
| Hematoma                                   | 10 (0.9%)           | 3 (0.3%)          | 0.091                |
| Occlusion, coronary artery                 | 1 (0.1%)            | 7 (0.7%)          | 0.039                |
| <b>Digestive System</b>                    | 14 (1.3%)           | 2 (0.2%)          | 0.004                |
| <b>Metabolic, Nutritional &amp; Immune</b> | 0 (0.0%)            | 1 (0.1%)          | 0.500                |
| <b>Nervous System/Psychiatric</b>          | 4 (0.4%)            | 4 (0.4%)          | 1.000                |
| <b>Respiratory System</b>                  | 4 (0.4%)            | 2 (0.2%)          | 0.687                |
| <b>Skin/Skin Appendage</b>                 | 4 (0.4%)            | 3 (0.3%)          | 1.000                |
| <b>Special Sense</b>                       | 7 (0.7%)            | 1 (0.1%)          | 1.000                |
| <b>Urogenital System</b>                   | 7 (0.7%)            | 1 (0.1%)          | 0.070                |

a. Data from NDA vol. 1.55, ref 11, table 31 and electronic datasets.

b. p value calculated using chi square test.

### 23.3 Bleeding in the RESTORE Trial

Table 23.3.4 Laboratory AEs leading to discontinuation, in the RESTORE trial<sup>a</sup>.

|                                            | Tirofiban<br>n=1071 | Placebo<br>n=1070 |
|--------------------------------------------|---------------------|-------------------|
| <b>Discontinued due to a laboratory AE</b> | 9 (0.8%)            | 2 (0.2%)          |
| <b>Bleeding lab AE</b>                     | 8 (0.7%)            | 2 (0.2%)          |

a. Data from NDA vol. 1.55, ref 11, table 32 and electronic datasets.

#### Bleeding AEs in the RESTORE trial

Overall, the sponsor stated that significantly more subjects in the tirofiban group had at least one episode of bleeding, when compared with placebo.

Table 23.3.5 (from table 6.2.3.13.2.5) Bleeding AEs in the RESTORE trial<sup>a</sup>.

|                                  | Tirofiban<br>n=1071 | Placebo<br>n=1070 | p value <sup>b</sup> |
|----------------------------------|---------------------|-------------------|----------------------|
| <b>Any bleeding complication</b> | 590 (55.1%)         | 434 (40.6%)       | <0.001               |
| <b>No bleeding complication</b>  | 481 (44.9%)         | 636 (59.4%)       |                      |

a. Data from NDA vol. 1.55, ref 11, table 35. Subjects with more than one AE were counted only once.

b. p value calculated using chi square test.

More subjects in the tirofiban group also had at least one episode of major bleeding, both by site and as judged by the TIMI classification.

Table 23.3.6 Major bleeding AEs in the RESTORE trial<sup>a</sup>.

|                                | Tirofiban<br>n=1071 | Placebo<br>n=1070 | p value <sup>b</sup> |
|--------------------------------|---------------------|-------------------|----------------------|
| <b>Major Bleeding:</b>         | 57 (5.3%)           | 40 (2.7%)         | 0.096                |
| Hemoglobin drop >5 g/dl        | 25 (2.3%)           | 19 (1.8%)         |                      |
| Transfusion of 2 units or more | 38 (3.5%)           | 24 (2.2%)         |                      |
| Corrective surgery             | 3 (0.3%)            | 2 (0.2%)          |                      |
| Intracranial hemorrhage        | 1 (0.1%)            | 3 (0.3%)          |                      |
| Retroperitoneal hemorrhage     | 6 (0.6%)            | 3 (0.3%)          |                      |
| <b>TIMI Bleeding: any</b>      | 156 (14.6%)         | 90 (8.4%)         | <0.001               |
| Major                          | 24 (2.2%)           | 17 (1.6%)         |                      |
| Minor                          | 129 (12.0%)         | 67 (6.3%)         |                      |
| Loss/ No site identified       | 3 (0.3%)            | 6 (0.6%)          |                      |

a. Data from NDA vol. 1.55, ref 11, table 36.

b. p value calculated using chi square test.

c. p value comparing the incidence of major bleeding only.

### 23.3 Bleeding in the RESTORE Trial

#### Sites of bleeding in the RESTORE trial

The sites for bleeding are summarized in the table below. Overall, tirofiban subject had significantly more bleeding at any site ( $p < 0.001$ ), at catheterization sites ( $p < 0.001$ ), hematomas ( $p < 0.001$ ), oral ( $p < 0.001$ ), nasal ( $p < 0.001$ ), GU/hematuria ( $p < 0.001$ ), and GI ( $p = 0.047$ ). There was one intracranial bleed in the tirofiban group, compared with two in the placebo group. There were five retroperitoneal bleeds in the tirofiban group compared with 3 in the placebo group.

Table 23.3.7 Major bleeding AEs in the RESTORE trial.

|                      | Tirofiban<br>n=1071 | Placebo<br>n=1070 | p-value |
|----------------------|---------------------|-------------------|---------|
| <b>Any site</b>      |                     |                   |         |
| Oozing               | 240 (22.4%)         | 172 (6.1%)        | <0.001  |
| Mild                 | 199 (18.6%)         | 171 (16.0%)       |         |
| Moderate             | 123 (18.6%)         | 74 (6.9%)         |         |
| Severe               | 21 (2.0%)           | 11 (1.0%)         |         |
| Life-threatening     | 7 (0.7%)            | 6 (0.6%)          |         |
| <b>IV site</b>       |                     |                   |         |
| Oozing               | 5 (0.5%)            | 3 (0.3%)          | 0.156   |
| Mild                 | 6 (0.6%)            | 3 (0.3%)          |         |
| Moderate             | 1 (0.1%)            | 1 (0.1%)          |         |
| Severe               | 0 (0%)              | 0 (0%)            |         |
| Life-threatening     | 0 (0%)              | 0 (0%)            |         |
| <b>Catheter site</b> |                     |                   |         |
| Oozing               | 335 (31.3%)         | 226 (21.1%)       | <0.001  |
| Mild                 | 45 (4.2%)           | 46 (4.3%)         |         |
| Moderate             | 37 (3.5%)           | 17 (1.6%)         |         |
| Severe               | 2 (0.2%)            | 2 (0.2%)          |         |
| Life-threatening     | 1 (0.1%)            | 0 (0%)            |         |
| <b>Hematoma</b>      |                     |                   |         |
| Oozing               | 5 (0.5%)            | 2 (0.2%)          | <0.001  |
| Mild                 | 95 (8.9%)           | 71 (6.6%)         |         |
| Moderate             | 69 (6.4%)           | 35 (3.3%)         |         |
| Severe               | 6 (0.6%)            | 3 (0.3%)          |         |
| Life-threatening     | 0 (0%)              | 1 (0%)            |         |
| <b>Oral</b>          |                     |                   |         |
| Oozing               | 13 (1.2%)           | 2 (0.2%)          | <0.001  |
| Mild                 | 22 (2.1%)           | 5 (0.5%)          |         |
| Moderate             | 1 (0.1%)            | 2 (0.2%)          |         |
| Severe               | 0 (0%)              | 0 (0%)            |         |
| Life-threatening     | 0 (0%)              | 0 (0%)            |         |
| <b>Nasal</b>         |                     |                   |         |
| Oozing               | 16 (1.5%)           | 1 (0.1%)          | <0.001  |
| Mild                 | 26 (2.4%)           | 4 (0.4%)          |         |
| Moderate             | 4 (0.4%)            | 0 (0%)            |         |
| Severe               | 0 (0%)              | 0 (0%)            |         |
| Life-threatening     | 0 (0%)              | 0 (0%)            |         |
| <b>GU/ Hematuria</b> |                     |                   |         |
| Oozing               | 9 (0.8%)            | 9 (0.8%)          | 0.022   |
| Mild                 | 77 (7.2%)           | 52 (4.9%)         |         |
| Moderate             | 25 (2.3%)           | 18 (1.7%)         |         |
| Severe               | 0 (0%)              | 3 (0.3%)          |         |
| Life-threatening     | 0 (0%)              | 0 (0%)            |         |

23.3 Bleeding in the RESTORE Trial

Table 23.3.7 Bleeding AEs grouped by site in the RESTORE trial<sup>a</sup>.

|                          | Tirofiban<br>n=1071 | Placebo<br>n=1070 | p-value |
|--------------------------|---------------------|-------------------|---------|
| <b>GI</b>                |                     |                   |         |
| Oozing                   | 1 (0.1%)            | 2 (0.2%)          | 0.047   |
| Mild                     | 16 (1.5%)           | 12 (1.1%)         |         |
| Moderate                 | 9 (0.8%)            | 3 (0.3%)          |         |
| Severe                   | 5 (0.5%)            | 1 (0.1%)          |         |
| Life-threatening         | 2 (0.2%)            | 1 (0.1%)          |         |
| <b>Hemoptysis</b>        |                     |                   |         |
| Oozing                   | 0 (0%)              | 0 (0%)            | 0.404   |
| Mild                     | 7 (0.7%)            | 5 (0.5%)          |         |
| Moderate                 | 1 (0.1%)            | 0 (0%)            |         |
| Severe                   | 0 (0%)              | 0 (0%)            |         |
| Life-threatening         | 0 (0%)              | 0 (0%)            |         |
| <b>Intracranial</b>      |                     |                   |         |
| Oozing                   | 0 (0%)              | 0 (0%)            | 0.317   |
| Mild                     | 0 (0%)              | 0 (0%)            |         |
| Moderate                 | 0 (0%)              | 0 (0%)            |         |
| Severe                   | 0 (0%)              | 0 (0%)            |         |
| Life-threatening         | 1 (0.1%)            | 2 (0.2%)          |         |
| <b>Retroperitoneal</b>   |                     |                   |         |
| Oozing                   | 0 (0%)              | 0 (0%)            | 0.319   |
| Mild                     | 1 (0.1%)            | 0 (0%)            |         |
| Moderate                 |                     |                   |         |
| Severe                   | 3 (0.3%)            | 1 (0.1%)          |         |
| Life-threatening         | 1 (0.1%)            | 2 (0.2%)          |         |
| <b>Other<sup>c</sup></b> |                     |                   |         |
| Oozing                   | 6 (0.6%)            | 0 (0%)            | 0.072   |
| Mild                     | 5 (0.5%)            | 5 (0.5%)          |         |
| Moderate                 | 0 (0%)              | 2 (0.2%)          |         |
| Severe                   | 1 (0.1%)            | 1 (0.1%)          |         |
| Life-threatening         | 3 (0.3%)            | 0 (0.3%)          |         |
| <b>Unknown</b>           |                     |                   |         |
| Oozing                   | 0 (0%)              | 2 (0.2%)          | 0.138   |
| Mild                     | 4 (0.4%)            | 11 (1.0%)         |         |
| Moderate                 | 5 (0.5%)            | 8 (0.7%)          |         |
| Severe                   | 4 (0.4%)            | 2 (0.2%)          |         |
| Life-threatening         | 0 (0%)              | 0 (0%)            |         |

a. Data from NDA vol. 1.55, ref 11, table 36. Definitions of categories can be found in section 8.1.5.3.

b. p value calculated using chi square test.

c. Other category Includes three subjects with pericardial bleeding, considered to be life-threatening.

23.3 Bleeding in the RESTORE Trial

**Transfusions in the RESTORE trial**

The results of the transfusion analyses for the RESTORE trial are summarized in the table below. The proportions of subjects requiring any transfusion and those requiring a transfusion of packed RBCs were higher in the tirofiban group than in the placebo group,  $p=0.031$  and  $p=0.049$ , respectively. There was no difference between treatments in the number of units of packed RBCs transfused. In the RESTORE trial, more subjects in the tirofiban +heparin group received transfusion of packed RBCs than in the placebo +heparin group: 43 (4.0%) vs. 22 (2.4%),  $p=0.049$ .

Table 23.3.5 Percent of subjects requiring transfusions in the RESTORE trial<sup>a</sup>.

| Type of transfusion | Tirofiban (N=1071) | Placebo (N=1070) | p-value |
|---------------------|--------------------|------------------|---------|
| Any Transfusion     |                    |                  | 0.031   |
| No                  | 1025 (95.7%)       | 1043 (97.5%)     |         |
| Yes                 | 46 (4.3%)          | 27 (2.5%)        |         |
| Whole Blood         |                    |                  | 1.000   |
| No                  | 1069 (99.8%)       | 1069 (99.9%)     |         |
| Yes                 | 2 (0.2%)           | 1 (0.1%)         |         |
| FFP                 |                    |                  | 1.000   |
| No                  | 1069 (99.8%)       | 1068 (99.8%)     |         |
| Yes                 | 2 (0.2%)           | 2 (0.2%)         |         |
| PRBC                |                    |                  | 0.049   |
| No                  | 1028 (96.0%)       | 1044 (97.6%)     |         |
| Yes                 | 43 (4.0%)          | 26 (2.4%)        |         |
| Cryoprecipitates    |                    |                  | 0.500   |
| No                  | 1071 (100.0%)      | 1069 (99.9%)     |         |
| Yes                 | 0 (0.0%)           | 1 (0.1%)         |         |
| Platelets           |                    |                  | 0.625   |
| No                  | 1070 (99.9%)       | 1068 (99.8%)     |         |
| Yes                 | 1 (0.1%)           | 2 (0.2%)         |         |
| Other               |                    |                  | 0.500   |
| No                  | 1069 (99.8%)       | 1070 (100.0%)    |         |
| Yes                 | 2 (0.2%)           | 0 (0.0%)         |         |

a. Data from sponsor at request of medical reviewer.

Table 23.3.6 Number of PRBC units transfused per subject in the RESTORE trial<sup>a</sup>.

|                  | Tirofiban (N=1071) | Placebo (N=1070) | p-value |
|------------------|--------------------|------------------|---------|
| PRBCs transfused | n (%)              | n (%)            |         |
| 0                | 1028 (96.0)        | 1044 (97.6)      | 0.854   |
| 1                | 7 (0.7)            | 3 (0.3)          |         |
| 2                | 20 (1.9)           | 13 (1.2)         |         |
| 3                | 3 (0.3)            | 2 (0.2)          |         |
| 4                | 5 (0.5)            | 5 (0.5)          |         |
| 5 or more units  | 8 (0.7)            | 3 (0.3)          |         |
| Mean             | 2.95 (---)         | 3.88 (---)       |         |

a. Data from sponsor at request of medical reviewer.

**24.0 Appendix Twelve: Listing of Subject Deaths in PRISM-PLUS Trial as of 11/17/95**

At the time the DSMB reviewed MRL's data on updated mortality figures (11/17/95), and the recommendation was made to drop the tirofiban alone arm, there were 23 patients who had died within 7 days of study start (14 tirofiban, 4 heparin, 5 combination); and 36 patients who had died within 30 days of study start (17 tirofiban, 12 heparin, 7 combination). Since all deaths were reported as serious adverse experiences, the DSMB received the MedWatch (FDA Form 3500) Reports on all these patients, and were unblinded to the treatment groups. The MedWatch reports included comprehensive narratives on the deaths as well as the reported causes of death as designated by the investigators. The two tables below, provided by the sponsor, list the subject #s and the causes of death for the patients who had died within 7 and 30 days of study start, respectively. The stated causes of death are per the sponsor, and have not been independently verified by the FDA. The majority of the deaths in both groups were ascribed to progressive or recurrent cardiovascular ischemia.

Table 24.0.1 Listing of subjects who die within 7 days (as of Nov. 17, 95) in the PRISM-PLUS trial<sup>a</sup>.

| Study Number           | AN   | Death (Rel Hour) | Cause of Death                                                 |
|------------------------|------|------------------|----------------------------------------------------------------|
| <b>Tirofiban Alone</b> |      |                  |                                                                |
| 006-008                | 5098 | 132              | Ischemic bowel, sepsis, s/p intra-aortic balloon               |
| 006-008                | 5146 | 41               | Recurrent chest pain, papillary muscle infarction              |
| 006-032                | 6623 | 98               | Cerebrovascular accident during angiography                    |
| 006-033                | 6131 | 96               | Angina, cardiogenic shock                                      |
| 006-033                | 6166 | 141              | Cardiac arrest during angiography                              |
| 006-034                | 6524 | 59               | Myocardial infarction, cardiogenic shock                       |
| 006-036                | 6236 | 119              | Pulmonary embolism, electro-mechanical dissociation            |
| 006-044                | 6250 | 91               | Mesenteric ischemia, electro-mechanical dissociation S/P, PTCA |
| 006-045                | 6057 | 107              | Recurrent chest pain, cardiogenic shock                        |
| 006-045                | 6290 | 67               | Sudden death                                                   |
| 006-053                | 5165 | 39               | Posterior myocardial infarction, cardiogenic shock             |
| 006-057                | 6615 | 79               | Myocardial infarction, cardiogenic shock                       |
| 006-067                | 5264 | 119              | Coronary bypass surgery, acute graft closure                   |
| 006-086                | 7530 | 89               | Ischemia heart failure cardiogenic shock                       |
| <b>Heparin</b>         |      |                  |                                                                |
| 006-008                | 5141 | 150              | Coronary bypass surgery, cardiogenic shock                     |
| 006-044                | 7079 | 22               | Cardiogenic shock                                              |
| 006-048                | 7248 | 67               | Myocardial infarction, cardiogenic shock                       |
| 006-059                | 6326 | 137              | Severe ischemia, cardiogenic shock                             |
| <b>Combination</b>     |      |                  |                                                                |
| 006-034                | 6906 | 120              | Inferior myocardial infarction, angiography, shock             |
| 006-037                | 6080 | 95               | Coronary bypass surgery, cardiogenic shock                     |
| 006-048                | 6430 | 123              | Sepsis, shock, electro-mechanical dissociation                 |
| 006-057                | 6564 | 108              | Sudden death                                                   |
| 006-092                | 7483 | 85               | PTCA, cardiogenic shock                                        |

a. Data from sponsor at request of medical officer, but not independently verified by FDA.

**24.0 Appendix Twelve: Listing of Subject Deaths in PRISM-PLUS Trial as of 11/17/95 (cont)**

-Table 24.0.1 Listing of subjects who died within 30 days (as of Nov. 17, 95) in the PRISM-PLUS trial.

| Study Number           | AN   | Death (Rel Day) | Cause of Death                                                 |
|------------------------|------|-----------------|----------------------------------------------------------------|
| <b>Tirofiban Alone</b> |      |                 |                                                                |
| 006-008                | 5098 | Day 6           | Ischemic bowel, sepsis, s/p intra-aortic balloon               |
| 006-008                | 5146 | Day 3           | Recurrent chest pain, papillary muscle infarction              |
| 006-032                | 6623 | Day 5           | Cerebrovascular accident during angiography                    |
| 006-033                | 6131 | Day 5           | Angina, cardiogenic shock                                      |
| 006-033                | 6166 | Day 7           | Cardiac arrest during angiography                              |
| 006-034                | 6524 | Day 3           | Myocardial infarction, cardiogenic shock                       |
| 006-034                | 6595 | Day 9           | Myocardial infarction                                          |
| 006-036                | 6236 | Day 6           | Pulmonary embolism, electro-mechanical dissociation            |
| 006-037                | 6340 | Day 10          | Electromechanical dissociation                                 |
| 006-044                | 6250 | Day 5           | Mesenteric ischemia, electro-mechanical dissociation S/P, PTCA |
| 006-045                | 6057 | Day 6           | Recurrent chest pain, cardiogenic shock                        |
| 006-045                | 6290 | Day 4           | Sudden death                                                   |
| 006-050                | 6547 | Day 8           | Shock and peri-CABG operative bleeding                         |
| 006-053                | 5165 | Day 3           | Posterior myocardial infarction, cardiogenic shock             |
| 006-057                | 6615 | Day 4           | Myocardial infarction, cardiogenic shock                       |
| 006-067                | 5264 | Day 6           | Coronary bypass surgery, acute graft closure                   |
| 006-086                | 7530 | Day 5           | Ischemia heart failure cardiogenic shock                       |
| <b>Heparin</b>         |      |                 |                                                                |
| 006-008                | 5141 | Day 7           | Coronary bypass surgery, cardiogenic shock                     |
| 006-042                | 6354 | Day 19          | MI/Pulmonary edema                                             |
| 006-043                | 6366 | Day 9           | Myocardial infarction                                          |
| 006-043                | 6676 | Day 18          | Electromechanical dissociation/Shock                           |
| 006-044                | 6126 | Day 19          | Unknown/possible cardiomyopathy                                |
| 006-044                | 6155 | Day 12          | Aortic dissection/intractable bleeding                         |
| 006-044                | 6818 | Day 21          | Pulmonary embolism                                             |
| 006-044                | 7079 | Day 2           | Cardiogenic shock                                              |
| 006-048                | 7248 | Day 4           | Myocardial infarction, cardiogenic shock                       |
| 006-059                | 6326 | Day 7           | Severe ischemia, cardiogenic shock                             |
| 006-09 1               | 7418 | Day 12          | Acute renal insufficiency/septicemia                           |
| 006-09 1               | 7423 | Day 17          | Circulatory collapse                                           |
| <b>Combination</b>     |      |                 |                                                                |
| 006-029                | 6473 | Day 17          | Sudden death                                                   |
| 006-034                | 6906 | Day 6           | Inferior myocardial infarction, angiography, shock             |
| 006-037                | 6080 | Day 5           | Coronary bypass surgery, cardiogenic shock                     |
| 006-048                | 6430 | Day 6           | Sepsis, shock, electromechanical dissociation                  |
| 006-049                | 6591 | Day 9           | Cardiogenic shock post-CABG                                    |
| 006-057                | 6564 | Day 6           | Sudden death                                                   |
| 006-092                | 7483 | Day 5           | PTCA, cardiogenic shock                                        |

Data from sponsor at request of medical officer, but not independently verified by FDA.

Note that the dropped arm document (Reference 57 in NDA 20,912) contains two additional deaths in Table 4 (AN 5 177 and 6695). These deaths occurred after the November 17, 1995 cut-off date referenced above (AN 5 177 died on November 25, 1995 and AN 6695 died December 9, 1996), and as such were not reviewed by the DSMB committee.