# ADVISORY COMMITTEE BRIEFING MATERIALS:
# AVAILABLE FOR PUBLIC RELEASE

Errata to the Amarin Pharmaceutical Ireland Limited (Amarin) Briefing Document for the Advisory Committee meeting on 14 November 2019. The erroneous text is identified by a strikethrough, with correction following in bold, unless otherwise specified.

1. Page 201; Data for Race in Table 39 corrected (see shaded table elements on next page). Data for "Missing" race was added (in bold text) and all other rows were shifted up into the correct category.

**Table 39. Demographic and Baseline Characteristics by Treatment and CV Risk Category Subrgoup: Established CVD Secondary and High-risk Primary Prevention Subgroups**

| | Secondary Prevention Subgroup | | | Primary Prevention Subgroup | | | |
|---|---|---|---|---|---|---|---|
| **Parameter Statistic** | **Icosapent Ethyl (N=2892)** | **Placebo (N=2893)** | **Overall (N=5785)** | **Icosapent Ethyl (N=1197)** | **Placebo (N=1197)** | **Overall (N=2394)** | **P-value[1]** |
| **Region** | | | | | | | <0.0001 |
| Westernized Region[2] | 1991 (68.8%) | 1990 (68.8%) | 3981 (68.8%) | 915 (76.4%) | 915 (76.4%) | 1830 (76.4%) | |
| Eastern European Region[3] | 833 (28.8%) | 834 (28.8%) | 1667 (28.8%) | 220 (18.4%) | 219 (18.3%) | 439 (18.3%) | |
| Asia Pacific Region[4] | 68 (2.4%) | 69 (2.4%) | 137 (2.4%) | 62 (5.2%) | 63 (5.3%) | 125 (5.2%) | |
| **Baseline Ezetimibe Use** | | | | | | | <0.0001 |
| Patients on Ezetimibe | 216 (7.5%) | 215 (7.4%) | 431 (7.5%) | 46 (3.8%) | 47 (3.9%) | 93 (3.9%) | |
| Patients not on Ezetimibe | 2676 (92.5%) | 2678 (92.6%) | 5354 (92.5%) | 1151 (96.2%) | 1150 (96.1%) | 2301 (96.1%) | |
| **Statin Intensity** | | | | | | | <0.0001 |
| Low | 113 (3.9%) | 126 (4.4%) | 239 (4.1%) | 141 (11.8%) | 141 (11.8%) | 282 (11.8%) | |
| Moderate | 1737 (60.1%) | 1753 (60.6%) | 3490 (60.3%) | 796 (66.5%) | 822 (68.7%) | 1618 (67.6%) | |
| High | 1038 (35.9%) | 999 (34.5%) | 2037 (35.2%) | 252 (21.1%) | 227 (19.0%) | 479 (20.0%) | |
| Data Missing | 4 (0.1%) | 15 (0.5%) | 19 (0.3%) | 8 (0.7%) | 7 (0.6%) | 15 (0.6%) | |
| **Age (years) at Randomization[5]** | | | | | | | 0.0147 |
| n | 2892 | 2893 | 5785 | 1197 | 1197 | 2394 | |
| Mean (SD) | 63.2 (8.69) | 63.3 (8.69) | 63.2 (8.69) | 63.7 (7.52) | 63.8 (7.75) | 63.7 (7.64) | |
| Median | 63.5 | 64.0 | 64.0 | 64.0 | 64.0 | 64.0 | |
| Min, Max | 45.0, 88.0 | 44.0, 91.0 | 44.0, 91.0 | 50.0, 92.0 | 50.0, 86.0 | 50.0, 92.0 | |
| **Sex, n (%)** | | | | | | | <0.0001 |
| Male | 2269 (78.5%) | 2267 (78.4%) | 4536 (78.4%) | 658 (55.0%) | 628 (52.5%) | 1286 (53.7%) | |
| Female | 623 (21.5%) | 626 (21.6%) | 1249 (21.6%) | 539 (45.0%) | 569 (47.5%) | 1108 (46.3%) | |
| **Race, n (%)** | | | | | | | <0.0001 |
| White | 2677 ( 92.6%) | 2675 ( 92.5%) | 5352 ( 92.5%) | 1014 ( 84.7%) | 1013 ( 84.6%) | 2027 ( 84.7%) | |
| Black Or African American | 26 ( 0.9%) | 47 ( 1.6%) | 73 ( 1.3%) | 43 ( 3.6%) | 42 ( 3.5%) | 85 ( 3.6%) | |
| Asian | 128 ( 4.4%) | 116 ( 4.0%) | 244 ( 4.2%) | 97 ( 8.1%) | 105 ( 8.8%) | 202 ( 8.4%) | |
| American Indian Or Alaska Native | 10 ( 0.3%) | 8 ( 0.3%) | 18 ( 0.3%) | 8 ( 0.7%) | 3 ( 0.3%) | 11 ( 0.5%) | |
| Native Hawaiian Or Other Pacific Islander | 6 ( 0.2%) | 2 ( 0.1%) | 8 ( 0.1%) | 1 ( 0.1%) | 1 ( 0.1%) | 2 ( 0.1%) | |
| Other | 23 ( 0.8%) | 15 ( 0.5%) | 38 ( 0.7%) | 7 ( 0.6%) | 20 ( 1.7%) | 27 ( 1.1%) | |
| Multiple | 22 ( 0.8%) | 29 ( 1.0%) | 51 ( 0.9%) | 27 ( 2.3%) | 13 ( 1.1%) | 40 ( 1.7%) | |
| **Missing** | **0** | **1 ( 0.0%)** | **1 ( 0.0%)** | **0** | **0** | **0** | |

2. Page 214; The title of Table 43 has been revised for accuracy by deleting "and Significantly Different (Full Cohort)".

**Table 43. Most Frequent TEAEs: ≥5% in Either Treatment Group ~~and Significantly Different (Full Cohort)~~; Reported by CV Risk: Secondary Prevention Subgroup (Safety Population)**

| Preferred Term [1], n (%) | Icosapent Ethyl (N=2892) | Placebo (N=2893) | p-value[2] |
|---|---|---|---|
| Hypertension | 235 (8.1%) | 229 (7.9%) | 0.77 |
| Diarrhoea | 228 (7.9%) | 299 (10.3%) | 0.001 |
| Back pain | 219 (7.6%) | 196 (6.8%) | 0.24 |
| Chest pain | 211 (7.3%) | 242 (8.4%) | 0.14 |
| Nasopharyngitis | 205 (7.1%) | 210 (7.3%) | 0.84 |
| Dyspnoea | 201 (7.0%) | 190 (6.6%) | 0.57 |
| Influenza | 200 (6.9%) | 211 (7.3%) | 0.61 |
| Pneumonia | 196 (6.8%) | 203 (7.0%) | 0.76 |
| Arthralgia | 190 (6.6%) | 190 (6.6%) | 1.00 |
| Oedema peripheral | 181 (6.3%) | 124 (4.3%) | 0.0008 |
| Bronchitis | 178 (6.2%) | 189 (6.5%) | 0.59 |
| Upper respiratory tract infection | 171 (5.9%) | 191 (6.6%) | 0.30 |
| Fatigue | 171 (5.9%) | 154 (5.3%) | 0.33 |
| Angina pectoris | 168 (5.8%) | 186 (6.4%) | 0.35 |
| Dizziness | 160 (5.5%) | 176 (6.1%) | 0.40 |
| Cough | 160 (5.5%) | 160 (5.5%) | 1.00 |
| Cataract | 156 (5.4%) | 146 (5.0%) | 0.56 |
| Pain in extremity | 155 (5.4%) | 160 (5.5%) | 0.82 |
| Atrial fibrillation | 155 (5.4%) | 123 (4.3%) | 0.05 |
| Osteoarthritis | 153 (5.3%) | 132 (4.6%) | 0.20 |
| Constipation | 149 (5.2%) | 103 (3.6%) | 0.003 |
| Anaemia | 114 (3.9%) | 156 (5.4%) | 0.01 |

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each subject, multiple TEAEs of the same Preferred Term will be counted only once within each Preferred Term.
TEAEs are listed in descending order of Icosapent Ethyl frequency. Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.
1 All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
2 Fishers Exact test.

3. Page 215; The title of Table 44 has been revised for accuracy by deleting "and Significantly Different (Full Cohort)".

**Table 44. Most Frequent TEAEs: ≥5% in Either Treatment Group ~~and Significantly Different (Full Cohort)~~; Reported by CV Risk: High-risk Primary Prevention Subgroup (Safety Population)**

| Preferred Term [1], n (%) | Icosapent Ethyl (N=2892) | Placebo (N=2893) | p-value[2] |
|---|---|---|---|
| Upper respiratory tract infection | 141 (11.8%) | 129 (10.8%) | 0.48 |
| Diarrhoea | 139 (11.6%) | 154 (12.9%) | 0.38 |
| Bronchitis | 128 (10.7%) | 111 (9.3%) | 0.28 |
| Arthralgia | 123 (10.3%) | 120 (10.0%) | 0.89 |
| Back pain | 116 (9.7%) | 113 (9.4%) | 0.89 |
| Urinary tract infection | 110 (9.2%) | 117 (9.8%) | 0.68 |
| Nasopharyngitis | 109 (9.1%) | 90 (7.5%) | 0.18 |
| Osteoarthritis | 88 (7.4%) | 86 (7.2%) | 0.94 |
| Oedema peripheral | 86 (7.2%) | 79 (6.6%) | 0.63 |
| Hypertension | 85 (7.1%) | 115 (9.6%) | 0.03 |
| Cough | 81 (6.8%) | 81 (6.8%) | 1.00 |
| Pain in extremity | 80 (6.7%) | 81 (6.8%) | 1.00 |
| Anaemia | 77 (6.4%) | 80 (6.7%) | 0.87 |
| Cataract | 77 (6.4%) | 62 (5.2%) | 0.22 |
| Dizziness | 75 (6.3%) | 70 (5.8%) | 0.73 |
| Constipation | 72 (6.0%) | 46 (3.8%) | 0.02 |
| Sinusitis | 69 (5.8%) | 65 (5.4%) | 0.79 |
| Pneumonia | 67 (5.6%) | 74 (6.2%) | 0.60 |
| Influenza | 63 (5.3%) | 60 (5.0%) | 0.85 |
| Fall | 63 (5.3%) | 54 (4.5%) | 0.45 |
| Type 2 diabetes mellitus | 62 (5.2%) | 57 (4.8%) | 0.71 |
| Chest pain | 62 (5.2%) | 48 (4.0%) | 0.20 |
| Musculoskeletal pain | 61 (5.1%) | 46 (3.8%) | 0.17 |
| Atrial fibrillation | 60 (5.0%) | 36 (3.0%) | 0.02 |
| Nausea | 57 (4.8%) | 65 (5.4%) | 0.52 |
| Diabetes mellitus | 53 (4.4%) | 60 (5.0%) | 0.56 |
| Headache | 52 (4.3%) | 61 (5.1%) | 0.44 |

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each subject, multiple TEAEs of the same Preferred Term will be counted only once within each Preferred Term.
TEAEs are listed in descending order of Icosapent Ethyl frequency. Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.
1 All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
2 Fishers Exact test.

4. Page 217; The column headers of Table 47 have been corrected to accurately define the number of high-risk primary prevention patients in each treatment group:

**Table 47. Anti-thrombotic Use in Patients with Bleeding TEAEs (Serious and Non-Serious) Including Hemorrhagic Stroke by CV Risk Category: High-risk Primary Prevention**

| Category<br>Medication | Icosapent Ethyl<br>(N=~~2892~~1197) | Placebo<br>(N=~~2893~~1197) | P-value |
|---|---|---|---|
| Subjects with at least one bleeding event | 147/1197 (12.3) | 120/1197 (10.0) | 0.0912 |
| Subjects on Anti-Platelet OR Anti-Coagulant at or before bleeding event | 123/ 147 (83.7) | 94/ 120 (78.3) | 0.2744 |
| Single Anti-Platelet: Aspirin Only | 69/ 147 (46.9) | 52/ 120 (43.3) | 0.6214 |
| >1 Anti-Platelet: Aspirin AND (Clopidogrel OR Prasugrel OR Ticagrelor) | 21/ 147 (14.3) | 10/ 120 (8.3) | 0.1784 |
| Anti-Coagulant: Warfarin OR Rivaroxaban OR Apixaban | 8/ 147 (5.4) | 7/ 120 (5.8) | 1.0000 |
| Both Anticoagulants Plus Any Anti-platelet listed above | 16/ 147 (10.9) | 14/ 120 (11.7) | 0.8481 |
| Subjects not on Anti-Platelet OR Anti-Coagulant at or before bleeding event | 24/ 147 (16.3) | 26/ 120 (21.7) | 0.2744 |

Note: Categories are mutually exclusive.
P-values are based on Fishers Exact test.

5. Page 218; The column headers of Table 49 have been corrected to accurately define the number of high-risk primary prevention patients in each treatment group:

**Table 49. Anti-thrombotic Use in Patients with Bleeding SAEs Including Hemorrhagic Stroke by CV Risk Category: High-risk Primary Prevention**

| Category<br>Medication | Icosapent Ethyl<br>(N=~~2892~~1197) | Placebo<br>(N=~~2893~~1197) | P-value |
|---|---|---|---|
| Subjects with at least one bleeding event | 31/1197 (2.6) | 26/1197 (2.2) | 0.5922 |
| Subjects on Anti-Platelet OR Anti-Coagulant at or before bleeding event | 29/ 31 (93.5) | 24/ 26 (92.3) | 1.0000 |
| Single Anti-Platelet: Aspirin Only | 7/ 31 (22.6) | 12/ 26 (46.2) | 0.0907 |
| >1 Anti-Platelet: Aspirin AND (Clopidogrel OR Prasugrel OR Ticagrelor) | 5/ 31 (16.1) | 1/ 26 (3.8) | 0.2046 |
| Anti-Coagulant: Warfarin OR Rivaroxaban OR Apixaban | 3/ 31 (9.7) | 3/ 26 (11.5) | 1.0000 |
| Both Anticoagulants Plus Any Anti-platelet listed above | 9/ 31 (29.0) | 5/ 26 (19.2) | 0.5392 |
| Subjects not on Anti-Platelet OR Anti-Coagulant at or before bleeding event | 2/ 31 (6.5) | 2/ 26 (7.7) | 1.0000 |

Note: Categories are mutually exclusive.
P-values are based on Fishers Exact test.

6. Page 233; The column headers of Tables 55 and 56 have been corrected to accurately define the number of patients in the Safety Population in each treatment group:

**Table 55. Anti-thrombotic Medication Use in Patients with Bleeding TEAEs (Serious and Non-Serious) Including Hemorrhagic Stroke (Safety Population)**

| Category<br>Medication | Icosapent Ethyl<br>(N=~~2892~~4089) | Placebo<br>(N=~~2893~~4090) | P-value |
|---|---|---|---|
| Subjects with at least one bleeding event | 494/4089 (12.1) | 412/4090 (10.1) | 0.0039 |
| Subjects on Anti-Platelet OR Anti-Coagulant at or before bleeding event | 464/ 494 (93.9) | 383/ 412 (93.0) | 0.5901 |
| Single Anti-Platelet: Aspirin Only | 196/ 494 (39.7) | 155/ 412 (37.6) | 0.5383 |
| >1 Anti-Platelet: Aspirin AND (Clopidogrel OR Prasugrel OR Ticagrelor) | 131/ 494 (26.5) | 120/ 412 (29.1) | 0.4124 |
| Anti-Coagulant: Warfarin OR Rivaroxaban OR Apixaban | 19/ 494 (3.8) | 19/ 412 (4.6) | 0.6193 |
| Both Anticoagulants Plus Any Anti-platelet listed above | 77/ 494 (15.6) | 53/ 412 (12.9) | 0.2548 |
| Subjects not on Anti-Platelet OR Anti-Coagulant at or before bleeding event | 30/ 494 (6.1) | 29/ 412 (7.0) | 0.5901 |

Note: Categories are mutually exclusive.
P-values are based on Fishers Exact test.

**Table 56. Anti-thrombotic Medication Use in Patients with Bleeding SAEs Including Hemorrhagic Stroke (Safety Population)**

| Category<br>Medication | Icosapent Ethyl<br>(N=~~2892~~4089) | Placebo<br>(N=~~2893~~4090) | P-value |
|---|---|---|---|
| Subjects with at least one bleeding event | 123/4089 (3.0) | 95/4090 (2.3) | 0.0549 |
| Subjects on Anti-Platelet OR Anti-Coagulant at or before bleeding event | 119/ 123 (96.7) | 93/ 95 (97.9) | 0.6988 |
| Single Anti-Platelet: Aspirin Only | 38/ 123 (30.9) | 25/ 95 (26.3) | 0.5470 |
| >1 Anti-Platelet: Aspirin AND (Clopidogrel OR Prasugrel OR Ticagrelor) | 31/ 123 (25.2) | 28/ 95 (29.5) | 0.5395 |
| Anti-Coagulant: Warfarin OR Rivaroxaban OR Apixaban | 6/ 123 (4.9) | 9/ 95 (9.5) | 0.2802 |
| Both Anticoagulants Plus Any Anti-platelet listed above | 30/ 123 (24.4) | 19/ 95 (20.0) | 0.5138 |
| Subjects not on Anti-Platelet OR Anti-Coagulant at or before bleeding event | 4/ 123 (3.3) | 2/ 95 (2.1) | 0.6988 |

Note: Categories are mutually exclusive.
P-values are based on Fishers Exact test.

7. Page 245; The column headers of Table 64 have been corrected to accurately define the number of patients in each treatment group.

**Table 64. Bleeding TEAEs Including Hemorrhagic Stroke in Patients without Baseline or Post-Baseline Atrial Fibrillation and/or Flutter**

| | **Icosapent Ethyl (N=~~449~~3640)** | **Placebo (N=~~443~~3647)** | **p-value[2]** |
|---|---|---|---|
| Bleeding related disorders[1] | 381 (10.5%) | 335 (9.2%) | 0.0702 |
| Gastrointestinal bleeding | 102 (2.8%) | 85 (2.3%) | 0.2086 |
| Central nervous system bleeding | 15 (0.4%) | 7 (0.2%) | 0.0924 |
| Hemorrhagic stroke | 10 (0.3%) | 9 (0.2%) | 0.8234 |
| Other bleeding | 285 (7.8%) | 263 (7.2%) | 0.3286 |

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
[1]Bleeding-related disorders are identified by the standardized MedDRA queries of "Gastrointestinal haemorrhage," "Central Nervous System haemorrhages and cerebrovascular conditions," and "Haemorrhage terms (excl laboratory terms)."
[2]Fishers Exact test.
Baseline: Atrial Fibrillation/Atrial Flutter history/AE (prerandomization)
Post-Baseline: Atrial Fibrillation or Flutter Requiring Hospitalization of ≥24 hours