

Muraglitazar Briefing Document, Safety
Endocrine and Metabolic Drugs Advisory Committee Meeting
September 9, 2005

NDA 21-865
Sponsor: Bristol Myers Squibb
Clinical Reviewer: Julie Golden, M.D.

Table of Contents

1	Abstract.....	2
2	Study Type and Design/Patient Enumeration.....	4
3	Extent of Exposure.....	7
4	Deaths.....	8
5	Other Serious Adverse Events.....	10
6	Dropouts and Other Significant Adverse Events.....	17
6.1	Overall profile of dropouts.....	17
6.2	Adverse events associated with dropouts.....	19
7	Significant Adverse Events And Laboratory Findings.....	22
7.1	Congestive Heart Failure.....	22
7.2	Cardiovascular Events.....	31
7.3	Edema.....	34
7.4	Hypoglycemia.....	38
7.5	Body Weight.....	40
7.6	Microscopic Hematuria/Bladder Cancer.....	43
7.7	Other Malignant Neoplasms.....	44
7.8	Hematologic Findings.....	46
7.8.1	Anemia.....	47
7.8.2	Neutropenia.....	48
7.9	Cholelithiasis.....	50
7.10	Liver Findings.....	50
7.11	Myopathy/Rhabdomyolysis/Creatine Kinase Elevation.....	55
8	Common Adverse Events.....	58
9	Vital Signs.....	60
9.1	Heart Rate.....	60
9.2	Blood Pressure.....	61
10	ECG Findings (QT _c).....	62
11	Clinical Pharmacology.....	69
12	Appendix.....	70

1 ABSTRACT

Muraglitazar is a novel compound; the first-in-class of dual peroxisome proliferative-activated receptors (PPARs) called glitazars. This drug targets the PPAR- γ and - α receptors, which are currently agonized separately in the thiazolidinediones for treatment of type 2 diabetes (pioglitazone and rosiglitazone, PPAR- γ), and the fibrates for treatment of dyslipidemia (fenofibrate and gemfibrozil, PPAR- α). Well-described adverse events with thiazolidinedione treatment include edema, congestive heart failure, and weight gain.¹ Therapy with fibrates is associated with cholelithiasis and creatine kinase elevation.² These safety issues were addressed by the applicant.

The safety database for muraglitazar includes 22 clinical pharmacology studies and six Phase 2 and 3 studies, including long term (up to two-year) extensions in several of the studies.

Important safety considerations identified with muraglitazar include the following:

- All-cause and cardiovascular mortality: An imbalance of total and cardiovascular deaths was noted in the muraglitazar clinical program, with 19 of 3226 (0.59%) deaths in muraglitazar-treated subjects (18 in type 2 diabetics, one in mixed dyslipidemics) as compared to two of 823 (0.24%) pioglitazone- and one of 591 (0.17%) placebo-treated subjects (all type 2 diabetics). There were nine (of 3226) cardiovascular deaths in muraglitazar-treated subjects, one (of 591) in the placebo group, and none (of 823) in the pioglitazone-treated subjects. The majority of cardiovascular deaths were seen in an active-controlled metformin add-on trial (5 of 587 [0.85%] of muraglitazar- versus 0 of 572 pioglitazone-treated subjects). The cardiovascular deaths seen in the clinical program were due to myocardial infarction, stroke, or sudden death. The majority of non-cardiovascular-related deaths were due to cancer.
- Heart failure: The incidence of investigator-reported congestive heart failure (CHF) in the muraglitazar-treated groups is greater than placebo and is dose-dependent. Subjects in the muraglitazar-treated groups experienced greater rates of serious adverse events of and discontinuations due to CHF than either comparator (particularly at higher doses than proposed for marketing), although the overall incidence of these events was low. Preliminary evaluation suggests that subjects randomized to muraglitazar 2.5 mg had similar rates of CHF to those randomized to pioglitazone 30 mg, and subjects on muraglitazar 5 mg had approximately double the rates of those on either muraglitazar 2.5 mg or pioglitazone 30 mg. A small proportion of events in the Phase 3 studies reported by the investigator as edema or dyspnea were determined to be CHF by an independent adjudication committee.

1 Nesto RW, et al. Thiazolidinedione Use, Fluid Retention, and Congestive Heart Failure: A Consensus Statement from the American Heart Association and American Diabetes Association. *Circulation* 2003 Dec 9;108(23): 2941-8.

2 Knopp RH. Drug Treatment of Lipid Disorders. *N Engl J Med* 1999 341: 498-511.

- Cardiovascular events, not including CHF: As with cardiovascular deaths, an imbalance in cardiovascular adverse events (defined as coronary disease and stroke) was seen in the Phase 2 and 3 studies pooled; primarily driven by the glyburide add-on study, in which there were 11 (of 384) cardiovascular-related AEs in the muraglitazar groups and none (of 199) in the placebo group. The other studies, while demonstrating a numerical increase in events in the muraglitazar groups over comparators, have too few events and too small a difference between groups to draw conclusions. Furthermore, a clear pattern in terms of a unifying diagnosis, common finding, or clinical presentation of these cardiovascular events has not emerged. Therefore, the risk of cardiovascular events with muraglitazar treatment (independent of fluid retention and congestive heart failure) is difficult to establish from the clinical studies.
- Edema: The incidence of edema in muraglitazar-treated subjects was greater than those on placebo, occurred in a dose-related fashion (with rates dramatically increasing at muraglitazar 10 and 20 mg), and increased with drug exposure. Although rates of edema varied widely between studies, subjects in the muraglitazar ≤ 5 mg group generally had similar rates of events to those in the pioglitazone ≤ 45 mg group.
- Carcinogenicity: Preclinical studies of muraglitazar and other PPAR agonists have revealed multi-site tumorigenesis in animals. In particular, a high incidence of transitional cell carcinoma of the bladder and kidney has been demonstrated in rodents at doses relevant to humans. The applicant has undertaken a screening program for microscopic hematuria and crystalluria in the Phase 3 clinical program, and has more broadly monitored the database for malignant neoplasms; however, the clinical significance of the pre-clinical findings has not been established at this time.
- Hematologic changes: Anemia and neutropenia are well-described PPAR- γ treatment-related effects, generally considered to be due to hemodilution from increased intravascular volume, although an increase in bone marrow fat has also been considered a potential contributor given the PPAR- γ effect on pre-adipocyte differentiation. A dose-related decrease in hematologic parameters was seen in the clinical program, with muraglitazar ≤ 5 mg having similar changes in hemoglobin to and a somewhat greater decrease in absolute neutrophil count than pioglitazone ≤ 45 mg. Adverse event rates of decreased absolute neutrophil count were slightly greater in the muraglitazar treatment groups than the comparators.
- Liver findings: Troglitazone, the first thiazolidinedione, was withdrawn from the market in 2000 due to idiosyncratic liver toxicity. Moreover, fibrates have rarely been associated with hepatitis. Although the clinical studies revealed no events of acute liver failure in any of the treatment groups, one subject in a Phase 1 clinical pharmacology study was discontinued due to an alanine aminotransferase (ALT) elevation approximately 8x ULN with unknown resolution. Two subjects in the

Phase 2 and 3 studies had ALT > 3x ULN and total bilirubin > 2 mg/dL; both were diagnosed with gallstones and had resolution of these laboratory abnormalities.

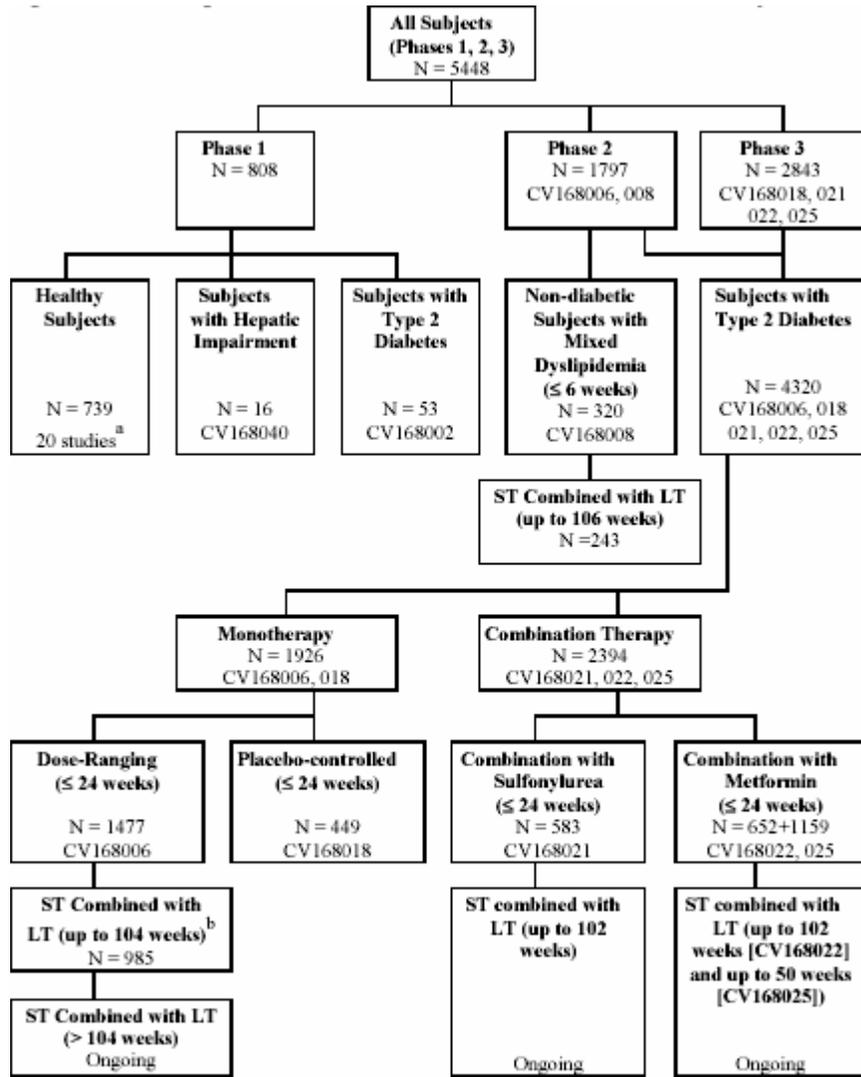
- Myopathy: The risk of myopathy with fibrate (PPAR- α) therapy is a known class effect, and incidence rises with concomitant statin use, commonly due to altered statin pharmacokinetics.³ In the muraglitazar studies, creatine kinase elevations greater than 10 times the upper limit of normal were similar across treatment groups, although there was a slightly higher rate of adverse and serious adverse events due to elevations in creatine kinase in the muraglitazar-treated group. There was one case of rhabdomyolysis in a subject on muraglitazar 5 mg in the long term phase of the glyburide add-on study.

2 STUDY TYPE AND DESIGN/PATIENT ENUMERATION

The safety database was comprised of 22 clinical pharmacology studies with a total of 808 healthy and type 2 diabetic subjects in the US and Japan (720 treated with muraglitazar), and six Phase 2b/3 studies with a total of 4640 type 2 diabetic and mixed dyslipidemic subjects (3226 treated with muraglitazar). Figure 2A represents the Phase 2 and 3 studies in the clinical program at the time of the initial NDA filing. There were five pivotal trials in subjects with type 2 diabetes (CV168006, -018, -021, -022, and -025), and one study in non-diabetic subjects with mixed dyslipidemia (CV168008). This review will present findings primarily from the type 2 diabetes pivotal studies.

³ Alsheikh-Ali AA, et al. Risk of adverse events with fibrates. *Am J Cardiol.* 2004 Oct 1;94(7):935-8.

Figure 2A. Muraglitazar Clinical Program and Number of Treated Subjects



^a CSR CV168001, 003, 004, 007, 009, 010, 011, 012, 013, 014, 015, 027, 037, 039, 041, 043, 044, 046, 047, 060

^b This is an interim analysis with data cutoff at 104 weeks; LT: Long-term; ST: Short-term

BMS summary_clinsafety Page 23

Study CV168006 (Phase 2; 24-week short term [ST], 104 wk long term [LT], 2 year LT extension) was a controlled, dose-ranging, dose-comparison, double-blind, randomized study with six treatment groups in drug-naïve subjects with type 2 diabetes: muraglitazar 0.5 mg, 1.5 mg, 5 mg, 10 mg, and 20 mg; and pioglitazone 15 mg. Subjects receiving muraglitazar 0.5 mg during the ST phase were reallocated to muraglitazar 1.5 at the beginning of the LT phase; all doses of study medication could have been titrated to the next higher dose up to a maximum of 20 mg for muraglitazar and 45 mg for pioglitazone. In the ST phase, subjects could have been rescued to the next higher dose as early as Week 6 and as late as Week 20.

Study CV168008 (Phase 2; 6 wk ST, 100 wk LT) was a placebo-controlled, dose-ranging, double-blind, randomized study with five treatment groups in non-diabetic

subjects with mixed dyslipidemia: muraglitazar 5 mg, 10 mg, 20 mg, and 20 mg + pravastatin 40 mg; and placebo. Subjects receiving muraglitazar 20 mg + pravastatin 40 mg during the ST phase were reallocated to muraglitazar 20 mg at the beginning of the LT phase.

Study CV168018 (Phase 3; 24 wk ST) was a double-blind, placebo-controlled, randomized, monotherapy study with three treatment groups in drug-naive subjects with type 2 diabetes: muraglitazar 2.5 mg and 5 mg; and placebo. In addition, there was an open-label (OL) cohort in which subjects who met the inclusion criteria and had a hemoglobin A1c value (HbA1c) > 10 to ≤ 12% received muraglitazar 5 mg.

Study CV168021 (Phase 3; 24 wk ST, 78 wk LT) was a double-blind, placebo-controlled, randomized, combination therapy study with three treatment groups in subjects with type 2 diabetes who were inadequately controlled on sulfonylurea therapy: muraglitazar 2.5 mg, muraglitazar 5 mg + glyburide, and placebo + glyburide. In the LT phase, subjects randomized to placebo could be rescued to muraglitazar 2.5 mg, and subjects randomized to muraglitazar 2.5 mg could be rescued to muraglitazar 5 mg if needed for glycemic control.

Study CV168022 (Phase 3; 24 wk ST, 78 wk LT) was a double-blind, placebo-controlled, randomized, combination therapy study with three treatment groups in subjects with type 2 diabetes who were inadequately controlled on metformin: muraglitazar 2.5 mg, muraglitazar 5 mg + metformin, and placebo + metformin. In the LT phase, subjects randomized to placebo could be rescued to muraglitazar 2.5 mg, and subjects randomized to muraglitazar 2.5 mg could be rescued to muraglitazar 5 mg if needed for glycemic control.

Study CV168025 (Phase 3; 24 wk ST, 26 wk LT) was a double-blind, active-controlled, randomized, combination therapy study with two treatment groups in subjects with type 2 diabetes who were inadequately controlled on metformin: muraglitazar 5 mg + metformin; pioglitazone 30 mg + metformin.

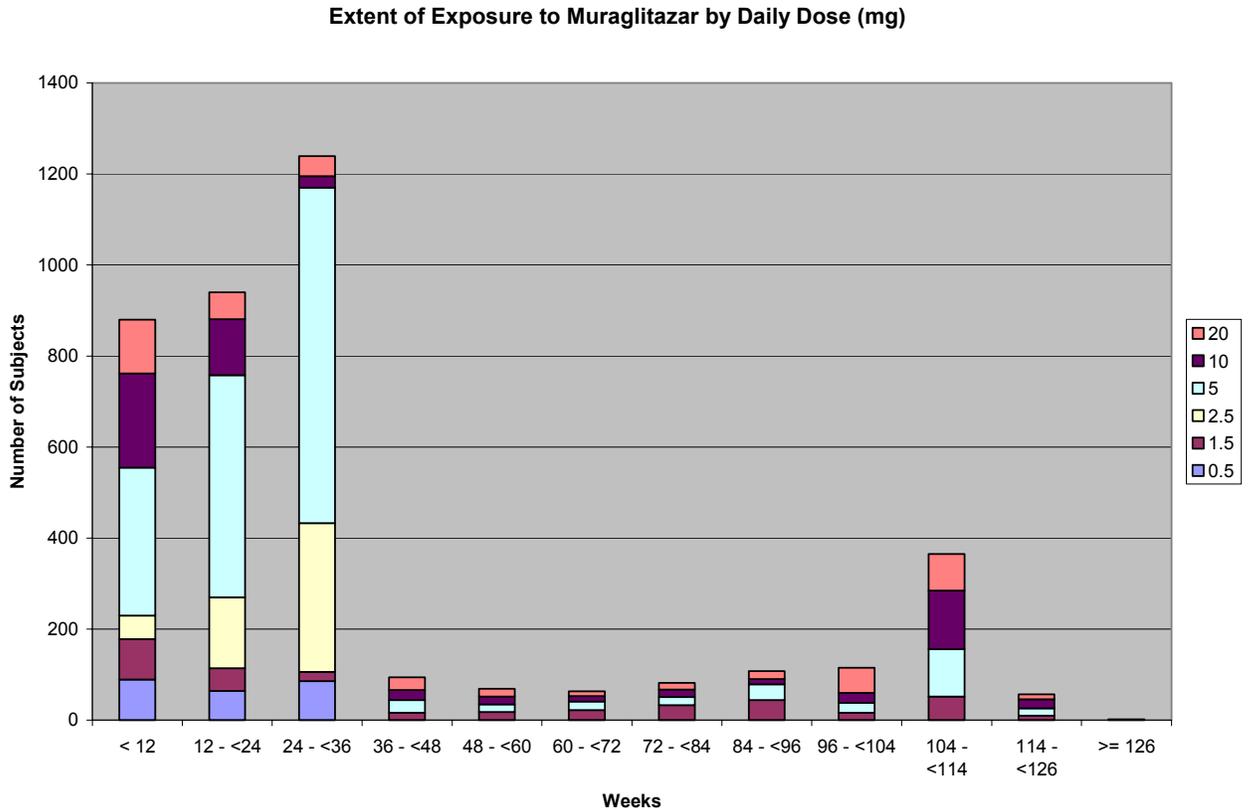
The data were pooled in a variety of ways; for the majority of the applicant's analyses, doses up to 5 mg of muraglitazar were compared with doses up to 45 mg of pioglitazone and placebo in the type 2 diabetes studies. In addition, monotherapy and combination therapy studies were analyzed separately when deemed clinically relevant. For deaths and rare events, all doses (including muraglitazar 10 and 20 mg in study CV168006) and all subjects (including mixed dyslipidemics in study CV168008) were combined to increase the denominator. This reviewer also evaluated selected events and laboratory findings separately by study because of important differences in design.

Long term study data were presented for study CV168006 in the NDA, and for studies CV168006, -021, and -022 in the 120-day Safety Update. Further analyses, including an interim analysis of the safety data for study CV168025 (50 weeks) were presented in an additional safety update late in the review cycle.

3 EXTENT OF EXPOSURE

The exposure to the various doses of muraglitazar for subjects in the Phase 2 and 3 studies is illustrated in Figure 3A. Because dose titration was permitted during the rescue period and LT double-blind extension phase in Study CV168006, subjects could be represented multiple times across doses. The number of subjects exposed to muraglitazar was highest for the 5 mg dose, either as initial treatment or after rescue or titration.

Figure 3A:



Within the applicant’s pooled group ‘muraglitazar \leq 5 mg’, a majority of subjects (86.5%) received the 2.5 or 5 mg dose of muraglitazar (22.5% and 64.0%, respectively). In addition, a total of 39.4% of subjects receiving muraglitazar 0.5 mg and 31.7% of subjects receiving muraglitazar 1.5 mg in this pooled group were titrated to 5 mg during the rescue period of the ST phase of study CV168006. In fact, only 6.0% and 7.5% of subjects in the muraglitazar \leq 5 mg group remained on muraglitazar 0.5 mg and 1.5 mg, respectively, for the duration of the ST phase. A total of 69.5% of subjects in the pooled group ‘pioglitazone \leq 45 mg’ received the 30 mg dose (study CV168025). A total of 9.6% of subjects in the pioglitazone \leq 45 mg group received 45 mg as a result of dose titration from pioglitazone 15 mg during the rescue period of the ST phase of study CV168006. The percentage of subjects that remained on pioglitazone 15 mg for the duration of the ST phase in the pioglitazone \leq 45 mg group was 20.9%.

The mean duration of exposure (weeks) in the ST phases was similar for muraglitazar monotherapy and combination therapy with glyburide and metformin. The proportion of subjects who completed at least 104 weeks of treatment during the LT extension phase of study CV168006 was 61.4% (282/459) in the muraglitazar group and 60.3% (88/146) in the pioglitazone group.

In the 120-day Safety Update, the number of type 2 diabetic subjects receiving any muraglitazar treatment increased from 2382 to 2513. This difference was because of subjects being titrated from placebo to muraglitazar in studies CV168021 and CV168022. The mean duration of exposure to muraglitazar for diabetic subjects increased from 47 to 59 weeks, with 21% of subjects exposed for 132 weeks or more in the Update, in contrast to less than 1% of subjects in the original NDA filing.

4 DEATHS

Twenty-two deaths in the muraglitazar clinical program have been reported to date; individual subject narratives can be found in the Appendix (Section 12). There were no deaths in any of the clinical pharmacology studies. Twenty-one deaths occurred in the type 2 diabetes pivotal studies, and one death occurred in the LT extension phase of study CV168008 (mixed dyslipidemia).

Table 4A enumerates the deaths by treatment group, and by all deaths and cardiovascular deaths. There were ten cardiovascular deaths in the clinical program; nine in the muraglitazar-treated subjects (9 of 3226; 0.28%) and one in placebo (1 of 591; 0.17%). There were no cardiovascular-related deaths in the pioglitazone-treated subjects (0 of 823). The majority of deaths occurred in subjects randomized to muraglitazar 5 mg (the treatment group with the largest number of subjects; please see Section 3).

Table 4A. Deaths in Muraglitazar Clinical Program							
Type 2 Diabetes	CV168006	MUR 0.5 N = 236	MUR 1.5 N = 259	MUR 5 N = 245	MUR 10 N = 249	MUR 20 N = 237	PIO 15 N = 251
	All Deaths	0	2	1	1	1	1
	Cardiovascular Deaths	0	0	0	0	1	0
	CV168018	MUR 2.5 N = 111	MUR 5 N = 114	PLACEBO N = 115			
	All Deaths	0	0	0			
	Cardiovascular Deaths	0	0	0			
	CV168021	MUR 2.5 + GLY N = 199	MUR 5 + GLY N = 191	PLACEBO + GLY N = 193			
	All Deaths	0	2	1			
	Cardiovascular Deaths	0	1	1			
	CV168022	MUR 2.5 + MET N = 233	MUR 5 + MET N = 205	PLACEBO + MET N = 214			
	All Deaths	2	3	0			
	Cardiovascular Deaths	1	1	0			
	CV168025	MUR 5 + MET N = 587	PIO 30 + MET N = 572				
	All Deaths	6	1				
Cardiovascular Deaths	5	0					
Mixed Dyslipidemia	CV168008	MUR 5	MUR 10	MUR 20	MUR 20 + PRAVA	PIO 15	
	All Deaths	0	0	0	1†	0	
	Cardiovascular Deaths	0	0	0	0	0	

† This subject was reallocated to muraglitazar 20 mg only at the LT phase of the study (the time of death).
MUR = muraglitazar, PIO = pioglitazone, GLY = glyburide, MET = metformin, NA = not applicable, ND = not done

Additional information with regards to the cardiovascular deaths:

- Mean exposure to the drug in these patients was 150.7 days (range: 10-307 days).
- Seven subjects were on concomitant metformin, and five were from a single study (CV168025).
- Four of nine cardiac deaths (myocardial infarctions) appear to have been temporally associated with heart failure. All four subjects had a significant history of vascular disease. Two events were preceded by symptoms of heart failure: one subject (muraglitazar 5 mg + glyburide) was hospitalized for CHF approximately 10 days prior to death, and the other subject (muraglitazar 5 mg + metformin) reportedly had symptoms of dyspnea due to heart decompensation the night before she died. One subject (muraglitazar 20 mg) presented with CHF due to a myocardial infarction; cardiac catheterization demonstrated a 99% left main arterial lesion. The fourth subject (muraglitazar 5 mg + glyburide) presented with an acute myocardial infarction and subsequently developed heart failure and other complications leading to death.

- Two events were classified as “sudden death”; both reportedly due to ischemic cardiac events (although autopsies were not performed). A third subject was “found dead” in his home; this was considered to be a cardiac death in a subject with known coronary artery disease.
- Two deaths were due to stroke.
- The one cardiovascular-related death in a placebo subject was due to a pulmonary embolism.

Causes of non-cardiovascular death include:

- Nine malignancies, including lung cancer (one subject on muraglitazar 1.5 mg and two subjects on muraglitazar 5 mg, all with history of tobacco use), acute myeloid leukemia (muraglitazar 1.5 mg), breast cancer (muraglitazar 5 mg), throat cancer (pioglitazone 15 mg), hepatic neoplasm (muraglitazar 2.5 mg), and pancreatic cancer (muraglitazar 5 mg). Rates of cancer deaths in the entire program were 8 of 3226 (0.25%) in the muraglitazar-treated subjects, 1 of 823 (0.12%) in the pioglitazone-treated subjects, and 0 of 591 in the placebo group.
- Two motor vehicle accidents in muraglitazar-treated subjects (10 and 20 mg monotherapy); apparently neither of which were caused by the subject.
- One gun shot wound (muraglitazar 5 mg) and one perforated ulcer (pioglitazone 30 mg).

5 OTHER SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) in the muraglitazar clinical program was defined as an adverse event that was fatal, life threatening, a congenital anomaly, an important medical event that jeopardized the subject or required intervention in order to prevent a serious outcome, or resulted in hospitalization or prolonged hospitalization, persistent or significant disability or incapacity, or development of drug dependency or abuse.

Short Term

The proportion of subjects experiencing SAEs on muraglitazar was higher relative to placebo- or pioglitazone-treated subjects. Table 5A, which utilizes the applicant’s pooling method (muraglitazar \leq 5 mg, pioglitazone \leq 45 mg, and placebo in the type 2 diabetes studies), demonstrates that the following System Organ Classes primarily account for the between group difference: *Cardiac Disorders; Nervous System Disorders; Injury, Poisoning and Procedural Complications; Neoplasms Benign, Malignant, and Unspecified; and Respiratory, Thoracic, and Mediastinal Disorders.*

	Any MUR ≤ 5 N=2374	Any PLA N=528	Any PIO ≤ 45 N=823
Total subjects with SAE	101 (4.3)	16 (3.0)	23 (2.8)
Cardiac Disorders	29 (1.2)	4 (0.8)	7 (0.9)
Nervous System Disorders	14 (0.6)	0	1 (0.1)
Injury, Poisoning, and Procedural Complications	12 (0.5)	1 (0.2)	2 (0.2)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	10 (0.4)	1 (0.2)	1 (0.1)
Gastrointestinal Disorders	9 (0.4)	1 (0.2)	6 (0.7)
Vascular Disorders	7 (0.3)	2 (0.4)	0
Infections and Infestations	6 (0.3)	4 (0.8)	3 (0.4)
Respiratory, Thoracic and Mediastinal Disorders	6 (0.3)	0	0
Hepatobiliary Disorders	5 (0.2)	1 (0.2)	0
General Disorders and Administration Site Conditions	4 (0.2)	1 (0.2)	1 (0.1)
Musculoskeletal and Connective Tissue Disorders	4 (0.2)	0	1 (0.1)
Metabolism and Nutrition Disorders	3 (0.1)	0	1 (0.1)
Renal and Urinary Disorders	3 (0.1)	1 (0.2)	2 (0.2)
Blood and Lymphatic System Disorders	2 (<0.1)	0	1 (0.1)
Endocrine Disorders	2 (<0.1)	0	0
Reproductive System and Breast Disorders	2 (<0.1)	1 (0.2)	1 (0.1)
Eye Disorders	1 (<0.1)	1 (0.2)	1 (0.1)
Investigations	1 (<0.1)	1 (0.2)	0

Adapted from BMS summary_clinsafety Page 283

Separate summaries of serious adverse events by ST monotherapy, combination with sulfonylurea, or combination with metformin are presented in the bulleted points and tables below. Please note that the tables are adapted from the applicant's tables, and include total subjects with SAEs as well as selected System Organ Classes of interest (e.g., most frequent, or more frequent than comparator).

- In the ST monotherapy studies (CV168006 and -018, Table 5B), the overall incidence of SAEs was higher in the muraglitazar 5 mg group (4.2%) than in the placebo or pioglitazone groups (2.6% and 3.2%, respectively). Across the treatment groups, SAEs occurred most commonly in the *Cardiac Disorders* SOC. Within each treatment group, none of the individual SAEs occurred in more than one subject.

	CV168006			CV168018			ALL
	MUR 1.5	MUR 5	PIO 15	MUR 2.5	MUR 5	PLA	MUR 5
	N = 259	N = 245	N = 251	N = 111	N = 114	N = 115	N = 359
Total Subjects With AE	10 (3.9)	12 (4.9)	8 (3.2)	4 (3.6)	3 (2.6)	3 (2.6)	15 (4.2)
Cardiac Disorders	1 (0.4)	2 (0.8)	2 (0.8)	1 (0.9)	2 (1.8)	1 (0.9)	4 (1.1)

Adapted from BMS summary_clinsafety, Page 293

- Study CV168006 (monotherapy, dose-ranging), also included doses above those proposed for marketing, muraglitazar 10 and 20 mg. SAEs were seen at the greatest frequency at the 10 mg dose (7.2%). Increased rates of *Cardiac Disorders* and *Nervous System Disorders* were seen at these higher doses (see Table 5C). There were two events each of atrial fibrillation, chest pain, and myocardial infarction in the

short term at these doses combined; all other Preferred Terms were only represented once.

Table 5C. Number (%) of Subjects with SAEs, CV168006 ST, All Doses						
	MUR 0.5	MUR 1.5	MUR 5	MUR 10	MUR 20	PIO 15
	N = 236	N = 259	N = 245	N = 249	N = 237	N = 251
Total Subjects With AE	4 (1.7)	10 (3.9)	11 (4.5)*	18 (7.2)	13 (5.5)	8 (3.2)
Cardiac Disorders	0	1 (0.4)	2 (0.8)	4 (1.6)	4 (1.7)	2 (0.8)
Nervous System Disorders	0	1 (0.4)	1 (0.4)	3 (1.2)	2 (0.8)	0

Adapted from BMS cv168006st, Page 2692

*Note: this value is different from the value in Table 5B (summary of clinical safety) for MUR 5 mg, because it appears that this table (5C, from the individual study CV168006 report) did not include one subject with an SAE of osteoarthritis.

- In the ST combination therapy with sulfonylurea study (CV168021), the overall incidence of SAEs was higher in subjects treated with muraglitazar in combination with glyburide (7.3% and 6.2% with muraglitazar 2.5 mg and muraglitazar 5 mg, respectively) than in those treated with placebo plus glyburide (1.5%). SAEs occurred most commonly in the *Cardiac Disorders* SOC (see Table 5D). Except for hypoglycemia in the muraglitazar 2.5 mg plus glyburide group (2 of 191 subjects; 1.0%) and cerebrovascular accident in the muraglitazar 5 mg plus glyburide group (2 of 193 subjects; 1.0%), none of the individual SAEs occurred in more than one subject.

Table 5D. Number (%) of Subjects with SAEs, Combination with Sulfonylurea			
	CV168021		
	MUR 2.5 + GLY	MUR 5 + GLY	PLA + GLY
	N = 191	N = 193	N = 199
Total Subjects With AE	14 (7.3)	12 (6.2)	3 (1.5)
Cardiac Disorders	3 (1.6)	5 (2.6)	1 (0.5)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1 (0.5)	2 (1.0)	0

Adapted from BMS summary_clinsafety, Page 301

- In the ST combination therapy with metformin studies (CV168022 and -025), the overall incidence of SAEs in combination with metformin therapy was 4.3% for muraglitazar 5 mg, 4.7% for placebo and 2.6% for pioglitazone 30 mg. Across the treatment groups, SAEs occurred most commonly in the *Cardiac Disorders* SOC (see Table 5E). None of the individual SAEs occurred in more than one subject except the following:
 - Two cases each of congestive cardiac failure, coronary artery atherosclerosis, and dyspnea in the muraglitazar group (2 of 792 subjects; 0.3%)
 - Two cases of subcutaneous abscess in the placebo group (2 of 214 subjects; 0.9%)
 - Two cases of atrial fibrillation in the pioglitazone 30 mg group (2 of 572 subjects; 0.3%)

Table 5E. Number (%) of Subjects with SAEs, Combination with Metformin						
	CV168022			CV168025		ALL
	MUR 2.5 + MET	MUR 5 + MET	PLA + MET	MUR 5 + MET	PIO 30 + MET	MUR 5 + MET
	N = 233	N = 205	N = 214	N = 587	N = 572	N = 792
Total Subjects With AE	8 (3.4)	11 (5.4)	10 (4.7)	23 (3.9)	15 (2.6)	34 (4.3)
Cardiac Disorders	4 (1.7)	3 (1.5)	2 (0.9)	8 (1.4)	5 (0.9)	11 (1.4)
Respiratory, Thoracic and Mediastinal Disorders	0	3 (1.5)	0	2 (0.3)	0	5 (0.6)
Nervous System Disorders	2 (0.9)	0	0	4 (0.7)	1 (0.2)	4 (0.5)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	0	1 (0.5)	0	2 (0.3)	1 (0.2)	3 (0.4)
Vascular Disorders	0	0	1 (0.5)	2 (0.3)	0	2 (0.3)

Adapted from BMS summary_clinsafety, Page 305

Because the most common SAEs were from the *Cardiac Disorders* SOC, this reviewer summarized SAEs by Preferred Term in this SOC by treatment group (Table 5F). All muraglitazar-treated subjects, including those at the muraglitazar 10 and 20 mg doses are included in this table. Subjects with a given PT are only counted once; the data are presented as N (%). The rate of events in this SOC was slightly higher than in the pioglitazone- and placebo-treated groups, in particular for myocardial infarction, unstable angina, and congestive heart failure (however if acute MI is included with the *myocardial infarction* Preferred Term, the rates are 0.3%, 0.1%, and 0.2% for muraglitazar-, pioglitazone-, and placebo-treated subjects, respectively).

Table 5F. SAEs in <i>Cardiac Disorders</i> SOC by Treatment Group, Type 2 Diabetes, ST			
Preferred Term	All MUR N = 2969	All PIO N = 823	All PLA N = 528
All Subjects	38 (1.3)	7 (0.9)	4 (0.8)
Myocardial Infarction	8 (0.3)	1 (0.1)	0
Angina Unstable	5 (0.2)	0	0
Atrial Fibrillation	4 (0.1)	2 (0.2)	0
Coronary Artery Disease	4 (0.1)	1 (0.1)	1 (0.2)
Cardiac Failure Congestive	4 (0.1)	0	0
Angina Pectoris	3 (0.1)	1 (0.1)	0
Myocardial Ischaemia	2 (0.1)	0	0
Coronary Artery Occlusion	2 (0.1)	0	1 (0.2)
Cor Pulmonale	2 (0.1)	0	0
Coronary Artery Atherosclerosis	2 (0.1)	0	0
Ventricular Tachycardia	1 (0.0)	0	1 (0.2)
Atrial Flutter	1 (0.0)	0	0
Atrioventricular Block Complete	1 (0.0)	0	0
Atrioventricular Block Second Degree	1 (0.0)	0	0
Cardiac Failure	1 (0.0)	0	0
Ventricular Extrasystoles	1 (0.0)	0	0
Cardiac Disorder	0	1 (0.1)	0
Ischaemic Cardiomyopathy	0	1 (0.1)	0
Supraventricular Extrasystoles	0	1 (0.1)	0
Acute Myocardial Infarction	0	0	1 (0.2)
Ventricular Arrhythmia	0	0	1 (0.2)

In addition to cardiac SAEs, this reviewer examined the SAE Preferred Terms (PT) under the *Nervous Systems Disorders* SOC, given the apparent higher rate of events in the muraglitazar-treated subjects versus placebo-treated subjects (0.6% versus 0, respectively, in the applicant’s pooling of muraglitazar \leq 5 mg). Table 5G demonstrates that the *Nervous Systems Disorders* SOC covers a wide variety of disorders, and no one Preferred Term clearly accounts for the discrepancy.

Table 5G. Nervous System Disorder SAEs by Preferred Term, Type 2 Diabetes, ST			
Preferred Term	All MUR N = 2969	All PIO N = 823	All PLA N = 528
All Subjects	19 (0.6)	1 (0.1)	0 (0.0)
Cerebrovascular Accident	4 (0.1)	1 (0.1)	0 (0.0)
Diabetic Neuropathy	2 (0.1)	0 (0.0)	0 (0.0)
Syncope	2 (0.1)	0 (0.0)	0 (0.0)
Carotid Artery Stenosis	1 (0.0)	0 (0.0)	0 (0.0)
Convulsion	1 (0.0)	0 (0.0)	0 (0.0)
Facial Palsy	1 (0.0)	0 (0.0)	0 (0.0)
Facial Paresis	1 (0.0)	0 (0.0)	0 (0.0)
Haemorrhagic Stroke	1 (0.0)	0 (0.0)	0 (0.0)
Hemiplegia	1 (0.0)	0 (0.0)	0 (0.0)
Nerve Root Compression	1 (0.0)	0 (0.0)	0 (0.0)
Radicular Syndrome	1 (0.0)	0 (0.0)	0 (0.0)
Sleep Apnoea Syndrome	1 (0.0)	0 (0.0)	0 (0.0)
Syncope Vasovagal	1 (0.0)	0 (0.0)	0 (0.0)
Transient Ischaemic Attack	1 (0.0)	0 (0.0)	0 (0.0)

In summary, muraglitazar-treated subjects have consistently higher rates of SAEs overall in the ST phase than either of the comparators. Many of the imbalances in individual SOCs (e.g., cardiac, neoplasm) are also seen when examining rates of non-serious and serious adverse events combined, and therefore will be discussed in Section 7. In addition, other individual SAEs by Preferred Term of importance, such as that of heart failure, will be discussed further in Section 7. It is noted that there were five subjects in the ST phase with SAEs of heart failure in the muraglitazar-treated subjects (Preferred Terms *cardiac failure* and *cardiac failure congestive*), and none in any of the comparator groups. The randomization of these subjects was: muraglitazar 2.5 mg (one subject), muraglitazar 5 mg (three subjects), and muraglitazar 20 mg (one subject).

Short Term Combined with Long Term

Table 5H describes the distribution of SAEs in subjects continuing into the long term (LT) phase of study CV168006. A similar proportion of subjects from each pooled group continued into the LT phase: muraglitazar \leq 5 mg, 459 of 2374 (19.3%) and pioglitazone \leq 45 mg, 146 of 823 (17.7%). The incidence of total SAEs during the combined ST and LT phase was moderately higher for muraglitazar than for pioglitazone.

System Organ Class (%)	Non-Titrated Dose		Initial or Titrated Dose	
	MUR 1.5 N = 75	MUR 5 N = 108	Any MUR ≤ 5 N = 459	Any PIO ≤ 45 N = 146
Total Subjects With AE	12 (16.0)	16 (14.8)	54 (11.8)	14 (9.6)
Cardiac Disorders	1 (1.3)	4 (3.7)	12 (2.6)	2 (1.4)
Gastrointestinal Disorders	2 (2.7)	1 (0.9)	8 (1.7)	4 (2.7)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	2 (2.7)	3 (2.8)	6 (1.3)	3 (2.1)
Renal And Urinary Disorders	2 (2.7)	0	5 (1.1)	1 (0.7)
Vascular Disorders	1 (1.3)	3 (2.8)	5 (1.1)	0
Hepatobiliary Disorders	2 (2.7)	2 (1.9)	4 (0.9)	0
Musculoskeletal And Connective Tissue Disorders	0	1 (0.9)	4 (0.9)	0
Nervous System Disorders	1 (1.3)	0	4 (0.9)	1 (0.7)
Infections and Infestations	0	2 (1.9)	3 (0.7)	1 (0.7)
Respiratory, Thoracic And Mediastinal Disorders	1 (1.3)	1 (0.9)	3 (0.7)	0
Endocrine Disorders	0	1 (0.9)	2 (0.4)	0
General Disorders And Administration Site Conditions	0	2 (1.9)	2 (0.4)	0
Injury, Poisoning And Procedural Complications	1 (1.3)	1 (0.9)	2 (0.4)	2 (1.4)
Reproductive System and Breast Disorders	0	1 (0.9)	2 (0.4)	1 (0.7)
Ear And Labyrinth Disorders	0	0	1 (0.2)	1 (0.7)
Investigations	0	0	1 (0.2)	0
Psychiatric Disorders	0	0	1 (0.2)	0
Eye Disorders	0	0	0	1 (0.7)

BMS summary_clinsafety, Page 311

The incidence of SAEs in the *Cardiac Disorders* SOC continued to be higher in the muraglitazar-treated subjects during the LT phase of the study (2.6% versus 1.4%). The incidence of SAEs in the Neoplasm SOC during the LT phase was higher on pioglitazone than on muraglitazar (2.1% versus 1.3%), whereas this was higher for muraglitazar during the ST phase (0.4% vs. 0.1%); however, the absolute number of subjects with neoplasm remained higher in the muraglitazar-treated group versus pioglitazone: 6 and 3, respectively).

The following tables present the rates of total and cardiac SAEs for those subjects achieving a maximum dose (Table 5I) and for those who were not titrated (Table 5J) in the ST and LT phases combined, including the higher doses of muraglitazar 10 and 20 mg.

	MUR Max 1.5 N = 121	MUR Max 5 N = 206	MUR Max 10 N = 274	MUR Max 20 N = 238	PIO Max 15 N = 64	PIO Max 45 N = 82
Total Subjects	13 (10.7)	31 (15.0)	45 (16.4)	34 (14.3)	8 (12.5)	6 (7.3)
Cardiac Disorders	1 (0.8)	10 (4.9)	6 (2.2)	12 (5.0)	1 (1.6)	1 (1.2)

Adapted from BMS cv168006lt, Page 3583

	MUR 1.5 N = 75	MUR 5 N = 108	MUR 10 N = 156	MUR 20 N = 75	PIO 15 N = 65
Total Subjects	12 (16.0)	16 (14.8)	30 (19.2)	15 (20.0)	8 (12.3)
Cardiac Disorders	1 (1.3)	4 (3.7)	4 (2.6)	6 (8.0)	1 (1.5)

Adapted from BMS cv168006lt, Page 3592

Safety Update

LT Monotherapy (study CV168006): There were small increases in the overall SAE incidence rates in each treatment group in the 120-day Update, relative to the original NDA filing, based on increased exposure. The total number of subjects with SAEs in the muraglitazar \leq 5 mg group was 54/459 (11.8%) at the time of the original filing, and 64/459 (13.9%) in the Update. There were 14/146 (9.6%) subjects with SAEs in the pioglitazone \leq 45 mg group in the original filing and 15/146 (10.3%) in the Update.

LT Combination Therapy with Sulfonylurea (study CV168021): The muraglitazar \leq 5 mg group SAE rate was similar to that of the non-titrated placebo group (8.8% versus 9.8%; please see Table 5K); however, the number of subjects continuing to the LT phase in the placebo group was less than that of the muraglitazar group, decreasing the denominator to a greater extent. Across the treatment groups, SAEs occurred most frequently (with incidences of 1% to 3%) in the Cardiac Disorder SOC, the Neoplasm SOC, and the Nervous System Disorder SOC. The overall incidence rates of cardiac SAEs increased over time for all treatment groups.

	Original NDA Submission			120-Day Safety Update			
	Mur 2.5 + Gly N= 191	Mur 5 + Gly N = 193	Pla + Gly N = 199	Non-Titrated Dose			Initial or Titrated Dose
				Mur 2.5 + Gly N=113	Mur 5 + Gly N=163	Pla + Gly N=51	Any Mur \leq 5 + Gly N=399
Total Subjects with SAE	14 (7.3)	12 (6.2)	3 (1.5)	14 (12.4)	16 (9.8)	5 (9.8)	35 (8.8)

Adapted from BMS safetyupdate, Page 59

LT Combination Therapy with Metformin: There were increases in the overall SAE incidence rates in each treatment group in the 120-day Update, relative to the NDA

(Table 5L). Additionally, as noted above in the sulfonylurea add-on study, the number of subjects continuing to the LT phase in the placebo group was less than that of the muraglitazar group, so the denominator decreased in the placebo group to a greater extent.

Table 5L. Number (%) of Subjects with SAEs - LT Combination with Metformin (CV168022)							
	Original NDA Submission			120-Day Safety Update			
				Non-Titrated Dose			Initial or Titrated Dose
	Mur 2.5 + Met	Mur 5 + Met	Pla + Met	Mur 2.5 + Met	Mur 5 + Met	Pla + Met	Any Mur ≤ 5 + Met
	N= 233	N = 205	N = 214	N=159	N=173	N=93	N=142
Total Subjects with SAE	8 (3.4)	11 (5.4)	10 (4.7)	15 (9.4)	15 (8.7)	12 (12.9)	34 (8.3)

Adapted from BMS safetyupdate, Page 65

6 DROPOUTS AND OTHER SIGNIFICANT ADVERSE EVENTS

6.1 Overall profile of dropouts

Short Term

Table 6.1.A presents subject dropout in the short term (ST) phase of the type 2 diabetes pivotal studies. The overall incidence of study discontinuation was lower for muraglitazar-treated than for pioglitazone- or placebo-treated subjects. A higher percentage of muraglitazar-treated subjects discontinued due to an adverse event, whereas there were more discontinuations due to lack of efficacy in the pioglitazone and placebo groups than in the muraglitazar group.

Table 6.1.A. Reasons for Study Discontinuation, Type 2 Diabetes Studies, ST Phase					
Study	Dose (mg)	Randomized (N)	Discontinuation Total (%)	Discontinuation AE (%)	Discontinuation Lack of Efficacy (%)
CV168006*	Mur 0.5	236	93 (39.4)	4 (1.7)	61 (25.8)
	Mur 1.5	259	84 (32.4)	11 (4.2)	42 (16.2)
	Mur 5	245	54 (22.0)	9 (3.7)	23 (9.4)
	Mur 10	249	53 (21.3)	23 (9.2)	9 (3.6)
	Mur 20	239	66 (27.6)	29 (12.1)	18 (7.5)
	Pio 15	251	94 (37.5)	12 (4.8)	58 (23.1)
CV168018	Mur 2.5	111	21 (18.9)	3 (2.7)	9 (8.1)
	Mur 5	114	22 (19.3)	4 (3.5)	10 (8.8)
	Placebo	115	42 (36.5)	3 (2.6)	32 (27.8)
	Mur 5 OL	109	48 (44.0)	4 (3.7)	27 (24.8)
CV168021	Mur 2.5+Gly	191	32 (16.8)	7 (3.7)	9 (4.7)
	Mur 5+Gly	193	27 (14.0)	11 (5.7)	8 (4.1)
	Placebo+Gly	199	60 (30.2)	4 (2.0)	41 (20.6)
CV168022	Mur2.5+Met	233	36 (15.5)	7 (3.0)	14 (6.0)
	Mur 5+Met	205	26 (12.7)	9 (4.4)	7 (3.4)
	Placebo+Met	214	63 (29.4)	4 (1.9)	33 (15.4)
CV168025	Mur 5+Met	587	65 (11.1)	15 (2.6)	18 (3.1)
	Pio 30+Met	572	90 (15.7)	8 (1.4)	36 (6.3)
Total	Mur 2.5	535	89 (16.6)	17 (3.2)	32 (6.0)
	Mur 5†	1344	194 (14.4)	48 (3.6)	66 (4.9)
	All Mur ≤ 5†	2374	460 (19.4)	80 (3.4)	201 (8.5)
	All Pio	823	184 (22.4)	20 (2.4)	94 (11.4)
	All Placebo	528	165 (31.3)	11 (2.1)	106 (20.1)

* Note that discontinuations by dose are by the subjects' original randomization, not rescue dose.

† Does not include Mur 5 OL cohort (CV168018).

Long Term

Table 6.1.B from the Safety Update presents the most updated subject disposition for the long term (LT) phases of studies CV168006, -021, and -022. As with the ST phase, subjects randomized to placebo were more likely to discontinue due to lack of efficacy, and subjects randomized to muraglitazar were more likely to discontinue due to an adverse event.

Table 6.1.B. Disposition of Subjects by Randomized Dose, LT Phase							
Study	Number Randomized	Number Started LT (%)	Completed or Ongoing in LT (%)	Discontinued in LT (%)	Reason for Discontinuation in LT		
					Adverse Events n	Lack of Efficacy n	Other n
CV168006							
MUR 0.5	236	136 (58)	104 (76)	32 (24)	8	8	16
MUR 1.5	259	166 (64)	126 (76)	40 (24)	13	2	25
MUR 5	245	182 (74)	130 (71)	52 (29)	16	4	32
MUR 10	249	191 (77)	137 (72)	54 (28)	19	10	25
MUR 20	239	164 (69)	99 (60)	65 (40)	34	7	24
PIO 15	251	146 (58)	87 (60)	59 (40)	5	32	22
CV168021							
MUR 2.5 + GLY	191	155 (81)	120 (77)	35 (23)	6	17	12
MUR 5 + GLY	193	163 (84)	108 (66)	55 (34)	7	30	18
PLA + GLY	199	132 (66)	76 (58)	56 (42)	1	42	13
CV168022							
MUR 2.5 + MET	233	189 (81)	154 (81)	35 (19)	5	15	15
MUR 5 + MET	205	173 (84)	142 (82)	31 (18)	8	14	9
PLA + MET	214	143 (67)	101 (71)	42 (29)	3	24	15
Data set: All Subjects Randomized							
* Includes subjects who never took study medication.							
** The number of subjects who started LT was used as the denominator to calculate %.							
***Other includes subject withdrew consent, death, lost to follow-up, poor/non-compliance, pregnancy, subject no longer meets study criteria, administrative reason by sponsor, and other.							

BMS safetyupdate, Page 43

6.2 Adverse events associated with dropouts

Discontinuations due to AEs were higher with muraglitazar than with pioglitazone or placebo in both the ST and LT phases, as noted above. This higher incidence can be explained by a greater incidence of discontinuations for edema, weight gain, hypoglycemia, and heart failure. As the applicant notes, some of these discontinuations were mandated by protocol, and are related to the pharmacologic and pharmacodynamic effects of muraglitazar.

Short Term

This reviewer summarized the number of subjects with the most common events by Preferred Term (PT) that led to study discontinuation by treatment group (Table 6.2.A). The applicant's listing of AEs leading to discontinuation can be found in Table 6.2.B. The reviewer's table combines all subjects (even at higher doses and in non-type 2 diabetic subjects) in the muraglitazar-treated group in order of frequency of PT. Adverse events such as peripheral edema, which occurred at very high incidence at the higher

doses of muraglitazar, led to an apparent higher rate of study discontinuations because of the inclusion of the higher doses in this table than is reflected in the applicant's table.

Table 6.2.A. Most Commonly Reported AEs Leading to Discontinuation in Muraglitazar-Treated Subjects, ST Phase, All Muraglitazar-Treated Subjects Combined, All Phase 2 and 3 Studies			
Preferred Term	All MUR N = 3226	All PIO N = 823	All PLA N = 591
Oedema Peripheral	44 (1.4)	1 (0.1)	2 (0.3)
Weight Increased	29 (0.9)	1 (0.1)	0 (0.0)
Cardiac Failure Congestive	8 (0.3)	1 (0.1)	0 (0.0)
Face Oedema	8 (0.3)	0 (0.0)	0 (0.0)
Dyspnoea	7 (0.2)	0 (0.0)	0 (0.0)
Generalised Oedema	7 (0.2)	0 (0.0)	0 (0.0)
Hypoglycaemia	7 (0.2)	0 (0.0)*	0 (0.0)
Neutropenia	7 (0.2)	0 (0.0)	0 (0.0)
Blood Creatine Phosphokinase Increased	6 (0.2)	0 (0.0)	0 (0.0)
Constipation	6 (0.2)	0 (0.0)	0 (0.0)
Myocardial Infarction	6 (0.2)	0 (0.0)	0 (0.0)
Arthralgia	5 (0.2)	0 (0.0)	0 (0.0)
Fatigue	5 (0.2)	0 (0.0)	0 (0.0)

* It should be noted that pioglitazone was not studied on a background of glyburide, where many of the hypoglycemia discontinuations were seen in the muraglitazar-treated groups.

Table 6.2.B using the applicant's pooling method (muraglitazar \leq 5 mg) demonstrates the most common AEs (\geq 0.1%) by System Organ Class and Preferred Term that led to discontinuation. Particular note is made of the increased incidence of discontinuations relative to comparator for *weight increased* and *cardiac failure congestive*, although the numbers were small. Additionally, note is made of an increased rate of discontinuations due to increased creatine kinase. This issue will be further discussed in Section 7.11.

Table 6.2.B. AEs Leading to Premature Discontinuation of Study Medication, Muraglitazar up to 5 mg Pooled (ST Phase)			
System Organ Class (%)	Any MUR ≤ 5	Any PLA	Any PIO ≤ 45
Preferred Term (%)	N = 2374	N = 528	N = 823
Total Subjects With AE	82 (3.5)	11 (2.1)	23 (2.8)
Investigations	16 (0.7)	2 (0.4)	4 (0.5)
Weight Increased	7 (0.3)	0	1 (0.1)
Blood Creatine Phosphokinase Increased	4 (0.2)	0	0
Cardiac Disorders	12 (0.5)	0	3 (0.4)
Cardiac Failure Congestive	5 (0.2)	0	1 (0.1)
Myocardial Infarction	3 (0.1)	0	0
Gastrointestinal Disorders	10 (0.4)	3 (0.6)	3 (0.4)
Constipation	4 (0.2)	0	0
Nausea	3 (0.1)	0	0
Vomiting	3 (0.1)	0	0
General Disorders And Administration Site Conditions	10 (0.4)	3 (0.6)	3 (0.4)
Oedema Peripheral	4 (0.2)	2 (0.4)	1 (0.1)
Fatigue	3 (0.1)	0	0
Nervous System Disorders	7 (0.3)	1 (0.2)	3 (0.4)
Blood And Lymphatic System Disorders	6 (0.3)	0	0
Neutropenia	3 (0.1)	0	0
Metabolism And Nutrition Disorders	6 (0.3)	1 (0.2)	2 (0.2)
Hypoglycaemia	6 (0.3)	0	0
Musculoskeletal And Connective Tissue Disorders	6 (0.3)	0	0
Arthralgia	3 (0.1)	0	0
Respiratory, Thoracic And Mediastinal Disorders	6 (0.3)	0	0
Infections And Infestations	5 (0.2)	0	0
Skin And Subcutaneous Tissue Disorders	5 (0.2)	0	0
Eye Disorders	3 (0.1)	1 (0.2)	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	3 (0.1)	1 (0.2)	1 (0.1)

BMS summary_clinsafety, Page 321

Long Term

In the applicant's presentation of subjects in study CV168006 who proceeded to the LT phase (Table 6.2.C), more subjects in the muraglitazar-treated group than in the pioglitazone-treated group discontinued due to adverse events overall, most notably for peripheral edema, pulmonary edema and congestive heart failure, cardiac disorders, and neoplasms.

Table 6.2.C. AEs Leading to Premature Discontinuation of Study Medication, LT Monotherapy				
	Non-titrated Dose (CV168006)		Initial or Titrated Dose (CV168006)	
	MUR 1.5	MUR 5	Any MUR ≤ 5	Any PIO ≤ 45
System Organ Class (%)				
Preferred Term (%)	N = 75	N = 108	N = 459	N = 146
Total Subjects With AE	8 (10.7)	10 (9.3)	26 (5.7)	5 (3.4)
General Disorders And Administration Site Conditions	0	1 (0.9)	6 (1.3)	1 (0.7)
Oedema Peripheral	0	1 (0.9)	6 (1.3)	1 (0.7)
Investigations	0	5 (4.6)	6 (1.3)	3 (2.1)
Weight Increased	0	5 (4.6)	5 (1.1)	2 (1.4)
Respiratory, Thoracic And Mediastinal Disorders	1 (1.3)	3 (2.8)	5 (1.1)	0
Pulmonary Oedema	0	2 (1.9)	2 (0.4)	0
Skin And Subcutaneous Tissue Disorders	1 (1.3)	1 (0.9)	4 (0.9)	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	2 (2.7)	1 (0.9)	3 (0.7)	0
Lung Neoplasm Malignant	1 (1.3)	0	1 (0.2)	0
Cardiac Disorders	1 (1.3)	1 (0.9)	2 (0.4)	0
Cardiac Failure Congestive	0	1 (0.9)	1 (0.2)	0
Palpitations	1 (1.3)	0	1 (0.2)	0
Gastrointestinal Disorders	1 (1.3)	0	2 (0.4)	0
Vomiting	1 (1.3)	0	1 (0.2)	0
Nervous System Disorders	1 (1.3)	0	2 (0.4)	0
Dizziness	1 (1.3)	0	2 (0.4)	0
Renal And Urinary Disorders	1 (1.3)	0	2 (0.4)	0
Renal Failure Acute	1 (1.3)	0	1 (0.2)	0
Blood And Lymphatic System Disorders	1 (1.3)	0	1 (0.2)	0
Neutropenia	1 (1.3)	0	1 (0.2)	0
Psychiatric Disorders	1 (1.3)	0	1 (0.2)	0
Alcoholism	1 (1.3)	0	1 (0.2)	0

BMS summary_clinsafety, Page 351

7 SIGNIFICANT ADVERSE EVENTS AND LABORATORY FINDINGS

7.1 Congestive Heart Failure

Congestive heart failure (CHF) is a known adverse effect of PPAR- γ agonists, likely as a result of volume overload, particularly in patients (type 2 diabetics) who are already susceptible to this effect. Patients with New York Heart Association (NYHA) Class III and IV cardiac status were not studied in muraglitazar clinical trials. The number of patients in muraglitazar Phase 3 clinical trials by New York Heart Association (NYHA) class at baseline is shown in Table 7.1.A, below; the overall incidence of baseline congestive heart failure in the Phase 3 studies was very low.

NYHA Functional Class	MUR 2.5 N = 535	MUR 5 N = 1208	PIO 30 N = 572	PLACEBO N = 528
None	531 (99.3)	1186 (98.2)	555 (97.0)	526 (99.6)
I	2 (< 0.5)	9 (0.7)	10 (1.7)	2 (< 0.5)
II	2 (< 0.5)	13 (1.1)	7 (1.2)	0
III	0	0	0	0
IV	0	0	0	0

BMS pharmacovigilance_plan, Page 13

Investigator-Reported

There were no reported events of CHF in the clinical pharmacology studies, although in study CV168034 (a Phase 2a, randomized, single-blind study in Japan) one event of new-onset cardiomegaly was noted in a subject receiving muraglitazar 10 mg for 42 days, leading to premature discontinuation. A brief narrative indicated that during the study period the cardiothoracic ratio (CTR) was increased to 55% from 44% at baseline, and then 42 and 84 days after study discontinuation the CTR decreased to 52% and 44%, respectively.

In the Phase 2 studies (CV168006 and -008), there were no events of CHF reported in the ST for doses of muraglitazar \leq 5 mg, pioglitazone, or placebo. In study CV168006 (ST), five subjects randomized to muraglitazar 10 mg, and two subjects randomized to muraglitazar 20 mg had investigator-reported AEs of CHF. One of these events in a subject on muraglitazar 20 mg was reported as an SAE, and three other subjects (two subjects on muraglitazar 10 mg and one on muraglitazar 20 mg) discontinued the study due to the CHF adverse event.

There were seven investigator-reported events of congestive heart failure in the Phase 3 studies. Table 7.1.B summarizes the incidence of CHF adverse events by study and dose.

Study	Dose (mg)	Randomized (N)	Subjects with CHF AEs (%)
CV168018	Mur 2.5	111	0
	Mur 5	114	0
	Placebo	115	0
	Mur 5 OL	109	0
CV168021	Mur 2.5+Gly	191	1 (0.5)
	Mur 5+Gly	193	1 (0.5)
	Placebo+Gly	199	0
CV168022	Mur 2.5+Met	233	0
	Mur 5+Met	205	1 (0.5)
	Placebo+Met	214	0
CV168025	Mur 5+Met	587	3 (0.5)
	Pio 30+Met	572	1 (0.2)

In the LT phase of study CV168006, two subjects on muraglitazar 5 mg, two subjects on muraglitazar 10 mg, and five subjects on muraglitazar 20 mg were reported to have heart

failure. These events are discussed further under the adjudication committee subsection. In study CV168008, in which non-diabetic subjects with mixed dyslipidemia were randomized to muraglitazar 5 mg, 10 mg, 20 mg, 20 mg/pravastatin 40 mg, or placebo, there were no events of heart failure reported in the ST (6 week) phase of the study, as noted above; however, in the LT phase, one subject randomized to muraglitazar 20 mg developed CHF after 92 days of treatment (study therapy had been discontinued after 86 days because of peripheral edema).

Table 7.1.C describes the incidence rates and number of subjects with investigator-reported heart failure events per 100 years of exposure, for all type 2 diabetic subjects at doses of muraglitazar 2.5 mg, muraglitazar 5 mg, placebo, or pioglitazone 30 mg in the Phase 3 studies and short-term phase of CV168006. There were no reported heart failure events for subjects in the muraglitazar 0.5 mg, muraglitazar 1.5 mg, or pioglitazone 15 mg groups. As noted previously, five subjects (1.6%) in the muraglitazar 10 mg, and two subjects (0.42%) in the muraglitazar 20 mg groups experienced CHF events during the ST phase.

Table 7.1.C. Incidence Rates and Number of Subjects with All Reported Heart Failure Event(s) Per 100 Years of Exposure, Subjects in Phase 3 Studies and Short-Term of CV168006					
		MUR 2.5	MUR 5	PLA	PIO 30
CV168018	Incidence	0/111	0/223	0/115	
	Yrs of Exposure	46.60	87.03	43.84	
	Subjects/100 Yrs	0	0	0	
CV168021	Incidence	1/191	1/193	0/199	
	Yrs of Exposure	79.04	83.53	77.91	
	Subjects/100 Yrs	1.27	1.20	0	
CV168022	Incidence	0/233	1/205	0/214	
	Yrs of Exposure	98.28	87.27	82.43	
	Subjects/100 Yrs	0	1.15	0	
CV168025	Incidence		3/587		1/572
	Yrs of Exposure		251.22		239.71
	Subjects/100 Yrs		1.19		0.42
CV168006 ST	Incidence		0/245		
	Yrs of Exposure		92.05		
	Subjects/100 Yrs		0		
Total	Incidence (%)	1/535 (0.19%)	5/1453 (0.34%)	0/528 (0%)	1/572 (0.17%)
	Yrs of Exposure	223.92	601.10	204.18	239.71
	Subjects/100 Yrs	0.45	0.83	0	0.42

BMS summary_clinsafety Page 94

Comments regarding the above:

- Heart failure was not reported at muraglitazar 2.5 mg or 5 mg in either of the ST monotherapy studies.
- Two subjects treated with muraglitazar (one at 2.5 mg and one at 5 mg) in combination with sulfonylurea had heart failure events; the event was considered an SAE in one case and the study drug was discontinued for both subjects.
- Four subjects treated with muraglitazar 5 mg in combination with metformin had heart failure events; the event was considered an SAE in three cases. The study drug was discontinued in three subjects.

- One subject treated with pioglitazone 30 mg in combination with metformin had a heart failure event; the event was not considered an SAE but the study drug was discontinued.
- Heart failure was not reported for subjects randomized to placebo treatment.

Adjudication Committee

An independent adjudication process to assess events of CHF was undertaken as part of the Phase 2 and 3 development program because its diagnosis may be undermined by bias; as the applicant notes, edema and weight gain with PPAR- γ agonist therapy may potentially lead to either over- or under-diagnosis. Moreover, intercurrent events such as myocardial infarction or arrhythmia, both of which are more common in diabetic patients than in the general population, may obscure potential drug-related effects.

The Phase 3 program utilized the adjudication process for all events described by a Preferred Term indicating heart failure, or a related term, such as dyspnea or edema (of moderate or greater intensity). The events were reviewed in a blinded fashion by the adjudication committee, comprised of three cardiologists not otherwise affiliated with the muraglitazar program. The committee had the following information available: subject characteristics, type of event, symptoms during the event, concomitant medications, medical attention sought for the event, physical findings, results of diagnostic tests [i.e., ECG, chest x-ray, echocardiogram, laboratory tests, (including NT-proBNP values obtained at baseline and at or near the time of the event in question)], diagnosis and treatments relevant to the event, medical history, event outcome, and a description of the course of the event. The following tables summarize the findings for the four Phase 3 studies; Table 7.1.B demonstrates that 13 of 53 events sent for adjudication were confirmed by the committee as heart failure.

Table 7.1.B. Heart Failure Adjudication Results for Protocols CV168018, CV168021, CV168022, and CV168025 by Number of Events and Number of Subjects for the Muraglitazar Treatment Group (N = 1743)			
	Number of Events/Subjects with Event Adjudicated	Number of Events/Subjects with Confirmed CHF by Adjudication	Number of Events/Subjects with Confirmed CHF by Adjudication Without an Intercurrent Event as Cause of Heart Failure
Heart Failure and Related Terms†	21 / 20	7 / 7	2 / 2
Edema and Related Terms‡	29 / 26	5 / 5	3 / 3
Multiple Preferred Terms with Same Onset Date*	3 / 3	1 / 1	1 / 1
Total	53 / 47	13 / 13	6 / 6

Adapted from BMS summary_clinsafety Page 504

† Includes Cardiac Failure, Cardiac Failure Congestive, Dyspnoea, Dyspnoea Exertional, and Pulmonary Congestion.

‡ Includes Face Oedema, Generalised Oedema, and Oedema Peripheral.

* Includes Cardiac Failure Congestive/Oedema Peripheral and Face Oedema/Oedema Peripheral

Table 7.1.C compares total confirmed (by adjudication) heart failure events between the treatment groups. The proportion of subjects with confirmed events is as follows: muraglitazar, 13/1743 = 0.75%; pioglitazone, 1/572 = 0.17%; and placebo, 0/528 = 0%. Of the 13 cases of confirmed CHF in muraglitazar-treated subjects, 11 were in subjects on muraglitazar 5 mg, and two were in subjects on muraglitazar 2.5 mg.

Protocol	Muraglitazar			Pioglitazone			Placebo		
	Number Treated	Confirmed Heart Failure N (%)	Confirmed Heart Failure, No Intercurrent Event N (%)	Number Treated	Confirmed Heart Failure N (%)	Confirmed Heart Failure, No Intercurrent Event N (%)	Number Treated	Confirmed Heart Failure N (%)	Confirmed Heart Failure, No Intercurrent Event N (%)
CV168018	334	1 (0.3%)	1 (0.3%)	0	NA	NA	115	0	0
CV168021	384	4 (1.0%)	1 (0.3%)	0	NA	NA	199	0	0
CV168022	438	1 (0.2%)	1 (0.2%)	0	NA	NA	214	0	0
CV168025	587	7 (1.2%)	3 (0.5%)	572	1 (0.2%)	1 (0.2%)	0	NA	NA

BMS summary_clinsafety Page 507

The adjudication committee confirmed the presence of heart failure for the six muraglitazar-treated subjects in the Phase 3 studies who were reported by the investigator to have heart failure. One event in a subject on pioglitazone with investigator-reported heart failure was not confirmed as CHF by the adjudication committee. The description of the events in these six subjects is as follows:

- Four events were determined to be due to an intercurrent event: heart block/bradycardia; adjustment of beta-blocker; accelerated hypertension; and aortic stenosis.
- Two heart failure events were not due to an intercurrent event. One of the two subjects was hospitalized, both were discontinued from the study therapy, and both were treated with diuretics. The heart failure events resolved two and seven days after onset.
 - One of these two subjects was believed by the committee to likely have heart failure at baseline.

The adjudication committee additionally confirmed the presence of heart failure for seven subjects with events that did not code specifically to the Preferred Terms of *cardiac failure congestive* or *cardiac failure*. Five of the 29 (17.2%) events with an edema-related Preferred Term were adjudicated as heart failure; four *oedema peripheral* of moderate or greater intensity, and one *generalised oedema*. Two of the 11 (18.2%) events with a Preferred Term of *dyspnoea* or *dyspnoea exertional* were adjudicated to be heart failure.

As a result of the Phase 3 adjudication process, the applicant drew the following conclusions (bulleted, italicized); the reviewer's comments follow.

- *Events identified by the investigator as heart failure are usually adjudicated as heart failure, indicating that over-diagnosis of heart failure by the investigators is not a common problem.*

- *Edema of moderate or greater intensity and dyspnea or dyspnea exertional of any intensity may represent heart failure in a small percentage of cases, indicating that heart failure may be under-diagnosed in these groups. The heart failure identified by the committee in subjects reported by the investigators to have edema or dyspnea appeared not to be severe as no subjects were hospitalized and study therapy was continued in most. These subjects were routinely treated with diuretics (as were subjects with investigator-identified heart failure) with resolution of the event, indicating that failure to identify these events as heart failure had little effect on subject treatment or outcome.*

Comment: It is conceivable that there were events that were neither identified as heart failure, nor submitted for adjudication (e.g., an unadjudicated event of ‘cough’ could potentially be an undiagnosed event of CHF). Although these events are likely to be few in number, the statement that “the failure to identify these events as heart failure had little effect on subject outcome” may be misleading, since on some level, this is unknown.

- *Intercurrent events are a common cause of heart failure in these studies. The adjudication committee indicated that 7 of the 14 events adjudicated to be heart failure were due to an intercurrent event.*

Comment: Because diabetic patients are highly predisposed to cardiovascular disease and resultant heart failure, one might expect similar rates of CHF associated with intercurrent events to be seen across treatment groups, including the placebo group. However, there were seven such events in the muraglitazar-treated groups, and none in either the pioglitazone- or placebo-treated groups. Nevertheless, this reviewer acknowledges that certain co-morbidities will predispose individuals to fluid retention and CHF upon exposure to PPAR- γ agonists.

- *The low number of heart failure events precludes identification of risk factors for the development of heart failure.*

Comment: This reviewer agrees that the overall number of heart failure events was low.

The Phase 2 process (studies CV168006 and -008) utilized a similar approach to Phase 3, with the exception that the only events adjudicated were those in which the Preferred Term explicitly indicated heart failure (cardiac failure congestive, cardiac failure, pulmonary edema, etc.). These terms, as in the Phase 3 process, were predefined. The committee’s review was blinded, with the exception of eight subjects for whom randomization was sent to the committee in error. There is no obvious evidence that the unblinding of these subjects impacted the results.

In the short-term phase of study CV168006, in which subjects with type 2 diabetes were randomized to receive muraglitazar 0.5 mg, 1.5 mg, 5 mg, 10 mg, 20 mg, or pioglitazone 15 mg, seven subjects had eight investigator-reported events of heart failure, five subjects on muraglitazar 10 mg and two subjects on muraglitazar 20 mg. Heart failure was confirmed by adjudication in four of the subjects receiving muraglitazar 10 mg (4/249 = 1.6%) and one subject receiving muraglitazar 20 mg (1/237 = 0.42%). The results of the adjudication are demonstrated below (Tables 7.1.D - 7.1.F):

Table 7.1.D. Subjects with Investigator-Identified Heart Failure Events During the Short-term Treatment Period Adjudicated Not to Have Heart Failure - CV168006				
Subject ID	Dose at Onset (mg)	Days on Therapy	Investigator Event Text	Adjudication Committee Comment on “No” Decision
CV168006-226-9	Mur 10	150	Congestive Heart Failure	“clear lungs on x-ray, normal BNP”
CV168006-252-3	Mur 10	50	Heart Failure	“absence of heart failure signs and symptoms”
CV168006-36-9	Mur 20	24	Congestive Heart Failure	“no physical findings other than shortness of breath, no NT-proBNP findings, no x-ray findings, clear lungs”

BMS summary_clinsafety, Page 519

Table 7.1.E. Subjects with Investigator-Identified Heart Failure Events During the Short-Term Treatment Period Adjudicated to Have Heart Failure Due to an Intercurrent Event - CV168006			
Subject ID	Dose at Onset (mg)	Days on Therapy	Adjudication Committee Identification of Intercurrent Event
CV168006-164-6	Mur 20	92	“non-Q-wave myocardial infarction”

BMS summary_clinsafety, Page 519

Table 7.1.F. Weight Gain, Treatment, and Time to Resolution of Events in Subjects Adjudicated to Have Heart Failure not Due to an Intercurrent Event - Short-Term Treatment Period CV168006							
Subject ID	Dose at Onset (mg)	Days on Therapy		Max Wgt Gain from Baseline to Event Onset	Treatment for Event	Days to Resolution of Event	
		At Event Onset	At Discontinuation			From Event Onset	From Discontinuation
CV168006-91-1	Mur 10	117	117	4.5 kg	Continue furosemide 40mg/day	22	22
CV168006-114-5	Mur 10	62	69	11.3 kg	none	25	18
CV168006-252-3	Mur 10	140	Not applicable	4.4 kg	Furosemide 20 mg/day	4	Not applicable
CV168006-280-3	Mur 10	88	88	4.0 kg	Increased furosemide from 20 mg/day to 40 mg/day	26	26

BMS summary_clinsafety, Page 520

The adjudication for the long-term phase of CV168006 was ongoing at the time of the initial filing. Table 7.1.G lists the results up to this time. Two subjects on muraglitazar 5 mg (2/206 = 1.0%), two subjects on muraglitazar 10 mg (2/274 = 0.73%), and five subjects on muraglitazar 20 mg (5/238 = 2.1%) had events adjudicated as heart failure.

Subject ID	Dose at Onset ^a (mg)	Days on Therapy	SAE (yes/no)	Discontinued (yes/no)	Intensity	Event Adjudicated as Heart Failure (yes/no) ^b	Intercurrent Event (yes/no) ^b	Heart Failure at Baseline ^b
CV168006-41-2	Post Mur 5	716	No	No	Mild	No	Not applicable	Not applicable
CV168006-85-1	Mur 5	365	No	Yes	Moderate	Yes	Yes	Unknown
CV168006-419-4	Post Mur 5	356	Yes	Yes	Severe	Yes	No	Unlikely
CV168006-34-3	Post Mur 10	868	Yes	Yes	Moderate	Yes	No	Unknown
CV168006-252-3 ^c	Post Mur 10	475	Yes	Yes	Severe	Yes	No	Unlikely
CV168006-38-4	Mur 20	351	No	No	Mild	Yes	No	Likely
CV168006-157-12	Mur 20	506	No	No	Severe	Yes	Yes	Unlikely
CV168006-163-4	Mur 20	557	Yes	Yes	Moderate	Yes	Yes	Unlikely
CV168006-164-6 ^c	Mur 20	190	Yes	Yes	Severe	Yes	No	Unknown
CV168006-291-9	Mur 20	390	Yes	No	Severe	Yes	No	Unlikely
	Post Mur 20	447	Yes	Yes	Severe	Yes	Yes	Unlikely

a "Post" indicates that events occurred after study drug was discontinued.
b Information derived from the supplemental case report form page "Heart Failure Adjudication"
c Subjects who also had investigator-identified heart failure events during the short-term treatment period

BMS summary_clinsafety Page 509

Three subjects with multiple events are worth noting:

- Subject CV168006-252-3 (muraglitazar 10 mg) had an investigator-reported event (based on edema and echocardiogram findings) in the ST that was not adjudicated as CHF on Day 50, and a second event on Day 140 that was adjudicated as CHF. On Day 475, she was hospitalized with an SAE of severe CHF that resolved with treatment and was discontinued from the study.
- Subject CV168006-164-6 (muraglitazar 20 mg) had an investigator-reported event in the ST phase that was adjudicated as CHF associated with an intercurrent event of non-Q-wave MI. On Day 121, the subject developed anemia and was treated with erythropoietin. On Day 148, he was hospitalized for a coronary artery bypass graft of

two vessels. This subject subsequently had an SAE of heart failure in the LT (Day 190, no intercurrent event) requiring hospitalization and study discontinuation.

- Subject CV168006-291-9 (muraglitazar 20 mg) presented with CHF on Day 390 at which time study medication was interrupted. Troponin levels were noted elevated on Day 400; study drug was reinstated on Day 404. On Day 416 his weight was 7.1 kg above baseline and his NT-proBNP had increased to 5101 from previous level of 71 on Day 331. On Day 422 a cardiac catheterization demonstrated 2-vessel disease and an apparent anterior wall infarct. Post-catheterization the subject developed hypotension and anemia. The study drug was restarted on Day 436 and then discontinued on Day 446. On Day 447 he was admitted for CHF and anemia, and again on Day 458 for acute coronary syndrome.

Safety Update

In the LT phase of studies CV168006, -021, or -022 presented in the Safety Update, there were four new events of congestive heart failure not previously reported; all in muraglitazar-treated subjects:

- Subject CV168006-101-5 (muraglitazar 10 mg): CHF was confirmed by the adjudication committee.
- Subject CV168006-245-27 (started on muraglitazar 1.5 mg; increased to 5 mg on Day 840 and then 10 mg on Day 924): CHF was confirmed by the adjudication committee. The committee considered it likely that CHF was present at baseline, and that there was an intercurrent event.
- Subject CV168021-55-2 (muraglitazar 2.5 mg + glyburide 15 mg): On Day 410, myocardial infarction and congestive cardiac failure were reported. A cardiac catheterization revealed significant 3-vessel disease and an ejection fraction of 30-35%. Coronary bypass graft surgery took place on Day 419. CHF was confirmed by the adjudication committee. The committee also considered the CHF due to an intercurrent event of myocardial infarction.
- Subject CV168021-237-5 (muraglitazar 5 mg + glyburide 10 mg): On Day 307, the subject experienced an acute myocardial infarction and consequently experienced SAEs of severe acute heart failure, atrial fibrillation twice, bradycardia, and ventricular fibrillation. The subject died on Day 321 (see Section 12, Appendix, for a narrative of this event). This event was not reported in time to be reviewed by the adjudication committee.

In summary, the incidence of investigator-reported CHF in the muraglitazar-treated groups appears to be greater than placebo and is dose-dependent. Furthermore, as noted in previous sections, subjects in the muraglitazar-treated groups experienced greater rates of SAEs and discontinuations due to CHF than either comparator, particularly at the higher doses. Preliminary evaluation suggests that subjects randomized to muraglitazar 2.5 mg had similar rates of investigator-reported CHF to those randomized to pioglitazone 30 mg, and subjects on muraglitazar 5 mg had approximately double the rates of either muraglitazar 2.5 mg or pioglitazone 30 mg. In the Phase 3 studies (muraglitazar 2.5 and 5 mg), a higher rate of heart failure events was reported and confirmed in subjects in the combination therapy studies, suggesting either an increased

risk with concomitant use of antihyperglycemic therapy, or a predisposition to the CHF effect of muraglitazar, possibly related to years of type 2 diabetes and resultant complications. Overall, incidence of CHF in the clinical program was low.

7.2 Cardiovascular Events

In the clinical pharmacology studies, incidence of adverse events under the System Organ Class (SOC) *Cardiac Disorders* was more frequent in subjects treated with muraglitazar than placebo (1.8% versus 1.0%); the majority of these findings were due to tachycardia. Please see Section 9.1 for further discussion of heart rate.

In the Phase 2 and 3 studies, the applicant reviewed the type 2 diabetes database for cardiovascular events (not including heart failure) by predefined Preferred Terms that were classified as coronary or cerebrovascular disease. Table 7.2.A demonstrates that the rate of cardiovascular events in the pooled muraglitazar-treated group was approximately double that of the pooled placebo- or pioglitazone-treated groups.

System Organ Class (%) Preferred Term (%)	All MUR ≤ 5 mg N = 2374	All PLA N = 528	All PIO ≤ 45 mg N = 823
Total Subjects With AE	33 (1.4)	4 (0.8)	6 (0.7)
Cardiac Disorders	26 (1.1)	4 (0.8)	5 (0.6)
Angina Pectoris	6 (0.3)	2 (0.4)	2 (0.2)
Myocardial Infarction	6 (0.3)	0	1 (0.1)
Angina Unstable	4 (0.2)	0	0
Myocardial Ischaemia	4 (0.2)	0	1 (0.1)
Coronary Artery Disease	3 (0.1)	1 (0.2)	2 (0.2)
Coronary Artery Atherosclerosis	2 (<0.1)	0	0
Coronary Artery Occlusion	2 (<0.1)	1 (0.2)	0
Acute Myocardial Infarction	0	1 (0.2)	0
Nervous System Disorders	7 (0.3)	0	1 (0.1)
Transient Ischaemic Attack	4 (0.2)	0	0
Cerebrovascular Accident	3 (0.1)	0	1 (0.1)
Haemorrhagic Stroke	1 (<0.1)	0	0

BMS summary_clinsafety Page 100

Because the difference in the incidence of cardiovascular events between muraglitazar and placebo in the ST phase is largely caused by an imbalance in these events in study CV168021 (add-on with glyburide), this reviewer has presented the data by the individual type 2 diabetes studies to further characterize events by Preferred Term and dose.

In the dose-ranging study (Table 7.2.B) cardiovascular-related events appear to be dose-related with no clear difference between muraglitazar 1.5 mg, muraglitazar 5 mg, and pioglitazone 15 mg. Rates increase at the muraglitazar 10 and 20 mg doses, although overall, the number of events is low.

Table 7.2.B. Cardiovascular Adverse Events, ST, Study CV168006						
	MUR 0.5 N = 236	MUR 1.5 N = 259	MUR 5 N = 245	MUR 10 N = 249	MUR 20 N = 237	PIO 15 N = 251
Total Subjects	0	2 (0.77)	2 (0.82)	3 (1.20)	4 (1.69)	2 (0.80)
Angina Pectoris	0	2 (0.77)	0	3 (1.20)	0	1 (0.40)
Angina Unstable	0	0	1 (0.41)	0	1 (0.42)	0
Cerebrovascular Accident	0	0	0	0	1 (0.42)	0
Coronary Artery Disease	0	0	0	0	1 (0.42)	1 (0.40)
Coronary Artery Occlusion	0	0	0	1 (0.40)	0	0
Myocardial Infarction	0	0	0	0	2 (0.84)	1 (0.40)
Myocardial Ischaemia	0	0	1 (0.41)	0	0	0
Transient Ischaemic Attack	0	0	1	0	0	0

In the placebo-controlled Phase 3 monotherapy study (Table 7.2.C) the numbers of events were too few to draw conclusions.

Table 7.2.C. Cardiovascular Adverse Events, ST, Study CV168018				
	MUR 2.5 N = 111	MUR 5 N = 114	PLACEBO N = 115	MUR 5 OL N = 109
Total Subjects	2 (1.80)	2 (1.75)	1 (0.87)	1 (0.92)
Acute Myocardial Infarction	0	0	1 (0.87)	0
Angina Pectoris	0	1 (0.88)	0	1 (0.92)
Coronary Artery Disease	1 (0.90)	0	0	0
Coronary Artery Occlusion	0	1 (0.88)	0	0
Haemorrhagic Stroke	1 (0.90)	0	0	0
Transient Ischaemic Attack	1 (0.90)	0	0	0

The glyburide add-on study CV168021 (Table 7.2.D), demonstrates an imbalance of events between muraglitazar and placebo groups (2.1%, 3.6%, and 0% in muraglitazar 2.5 mg, muraglitazar 5 mg, and placebo, respectively). The applicant's analysis of coronary and cerebrovascular events per 1000 subject-years of exposure during the ST/ST+LT phase at first onset of event was 54.23 in the muraglitazar 2.5 mg + glyburide group, 63.58 in the muraglitazar 5 mg + glyburide group, and 24.27 in the placebo + glyburide group. The possibility of an adverse interaction between muraglitazar and glyburide has been considered; however, Phase 1 pharmacokinetic testing with glyburide did not indicate any changes in pharmacokinetic parameters, nor increased cardiovascular adverse events (although sample size was small). It may be that baseline characteristics, including length of time with type 2 diabetes, may make these individuals more susceptible to cardiovascular events with this drug.

Cardiovascular events in this study were divided between coronary and cerebrovascular events, indicating no clear pattern. Furthermore, there were three serious adverse events in this study identified by the reviewer as highly questionable as to the relationship to study drug:

- Subject CV168021-217-13 (muraglitazar 5 mg + glyburide) experienced an SAE of cerebrovascular accident on study Day 26. On Day 43 the subject was diagnosed with a non-operable brain tumor, which was reported as the cause of the cerebrovascular accident.

- Subject CV168021-243-7 (muraglitazar 5 mg + glyburide) experienced an SAE of large-focal myocardial infarction of study Day 1, prior to the first dose of study drug (revealed by changes on the Day 1 electrocardiogram). The subject was hospitalized on Day 2. Study medication was administered for a total of one day.
- Subject CV168021-244-1 (muraglitazar 2.5 mg + glyburide) had an ECG on Day 1 that was significant for sinus bradycardia, right bundle branch block, left ventricular hypertrophy, slow intra-atrial conduction, and worsening of repolarization. CK (536 IU/L) and CK/MB (5.9 µg/L) levels were also elevated on Day 1 from the preceding placebo lead-in period. It appears that these Day 1 events occurred before the drug was first administered, although the details are vague. The subject was hospitalized for unstable angina on study Day 11 after a cardiologist was consulted.

	MUR 2.5 N = 191	MUR 5 N = 193	PLACEBO N = 199
Total Subjects	4 (2.09)	7 (3.63)	0
Angina Pectoris	0	1 (0.52)	0
Angina Unstable	1 (0.52)	0	0
Cerebrovascular Accident	1 (0.52)	2 (1.04)	0
Coronary Artery Disease	0	1 (0.52)	0
Myocardial Infarction	1 (0.52)	1 (0.52)	0
Myocardial Ischaemia	0	1 (0.52)	0
Transient Ischaemic Attack	1 (0.52)	1 (0.52)	0

In the placebo-controlled metformin add-on study (Table 7.2.E) similar numbers of events occurred between groups, with a slightly higher rate (2.2%) of events in the muraglitazar 2.5 mg group, as compared to muraglitazar 5 mg (1.5%) and placebo (1.4%) groups. However, the applicant's analysis of coronary and cerebrovascular events per 1000 subject-years of exposure during the ST/ST+LT phase at first onset of event was 30.63 in the muraglitazar 2.5 mg + glyburide group, 33.90 in the muraglitazar 5 mg + glyburide group, and 37.00 in the placebo + glyburide group, indicating no increased risk of cardiovascular events in this study when analyzed by exposure over the long term.

	MUR 2.5 N = 233	MUR 5 N = 205	PLACEBO N = 214
Total Subjects	5 (2.15)	3 (1.46)	3 (1.40)
Angina Pectoris	0	0	2 (0.93)
Angina Unstable	1 (0.43)	0	0
Coronary Artery Atherosclerosis	0	1 (0.49)	0
Coronary Artery Disease	0	0	1 (0.47)
Coronary Artery Occlusion	1 (0.43)	0	1 (0.47)
Myocardial Infarction	3 (1.29)	1 (0.49)	0
Myocardial Ischaemia	0	1 (0.49)	0

Finally, the metformin add-on, active-controlled trial comparing muraglitazar 5 mg to pioglitazone 30 mg (Table 7.2.F), revealed a small numerical difference in cardiovascular events between groups. However, as discussed in Section 4, cardiovascular death

incidence in the 50-week analysis of this trial demonstrated the muraglitazar-treatment group was greater than the pioglitazone-treatment group (5 versus 0).

Table 7.2.F. Cardiovascular Adverse Events, ST, Study CV168025		
	MUR 5 N = 587	PIO 30 N = 572
Total Subjects	6 (1.02)	4 (0.70)
Angina Pectoris	2 (0.34)	1 (0.17)
Angina Unstable	1 (0.17)	0
Cerebrovascular Accident	0	1 (0.17)
Coronary Artery Atherosclerosis	1 (0.17)	0
Coronary Artery Disease	1 (0.17)	1 (0.17)
Myocardial Ischaemia	1 (0.17)	1 (0.17)

In the long-term (LT) phase of study CV168006, the applicant's analysis of those subjects randomized to muraglitazar \leq 5 mg revealed that the incidence of cardiovascular events was slightly higher for muraglitazar than pioglitazone: 14 of 459 subjects (3.1%) for muraglitazar, and 4 of 146 subjects (2.7%) for pioglitazone; however, because more muraglitazar-treated subjects discontinued due to an adverse event than pioglitazone-treated subjects, some degree of drop-out bias (in favor of muraglitazar) may be present.

Because of the inconsistencies between studies, these results are difficult to interpret, and the clinical significance is unclear. Although the cardiovascular event rate difference between groups is demonstrated when the studies are pooled (Table 7.2.A), when examining the studies individually, the glyburide combination study drove the discrepant overall cardiovascular event rate, and the active-control metformin combination study drove the discrepant cardiovascular death rate. Furthermore, it is difficult to find a unifying diagnosis to explain these events, as most cardiovascular events did not appear to coincide with events of heart failure or fluid overload.

7.3 Edema

Clinical experience with other PPAR- γ compounds indicates that edema is a common treatment-related adverse event. The etiology is somewhat unclear, although increased vasodilation and reduced renal sodium excretion have been proposed as potential mechanisms. Edema is highly correlated with insulin-sensitizing efficacy, and as such, may be considered a PPAR- γ pharmacodynamic effect.

Clinical Pharmacology

In the clinical pharmacology studies edema was more frequent in the muraglitazar-treated subjects than comparator: 15 adverse events of peripheral edema (2.2% of subjects) were observed in subjects treated with muraglitazar (either alone or in combination with active agents), and no events of edema in subjects receiving an active agent alone or placebo. When all adverse events of edema or swelling (peripheral edema, eyelid edema, eye swelling, generalized edema, fluid retention, joint swelling, face swelling, and face edema) were considered together, there were 23 occurrences in 20 of the 678 subjects (2.9%) treated with either muraglitazar alone or in combination, two events in two

subjects (0.7%) on Active Other, and two events in two subjects (2.0%) on placebo. Peripheral edema adverse events were seen when muraglitazar doses of 20 mg to 50 mg were given for 1 to 4 weeks. There were no events of peripheral edema in either diabetic or healthy subjects who received muraglitazar 5 mg once daily for 28 days.

Short Term, Phase 2 and 3

The Phase 2 dose-ranging study utilized a different approach in collecting adverse events of edema than the Phase 3 studies. In study CV168006, edema-related AEs were collected based on investigator monitoring for bilateral lower extremity edema at each visit; in Phase 3 studies (CV168018, -021, -022, and -025), edema-related AEs were collected as spontaneous reporting by the subject and/or investigator.

In the Phase 2 and 3 studies (see Table 7.3.A), the incidence of edema events in muraglitazar-treated subjects was generally dose-dependent (please note that subjects randomized to the lower doses of study CV168006 may have been exposed by rescue to higher doses), and greater than placebo. Additionally, the incidence and severity of edema dramatically increased at the muraglitazar 10 and 20 mg doses.

Table 7.3.A. Number (%) of Subjects with Edema-related AEs, Total and by Intensity, ST Type 2 Diabetes Studies							
Study	Dose (mg)	N	Subjects with Edema AE (%)	Edema Adverse Events by Treatment Group and Highest Severity			
				Mild	Moderate	Severe	Very Severe
CV168006	Mur 0.5	236	25 (10.6)	19 (8.1)	6 (2.5)	0	0
	Mur 1.5	259	25 (9.7)	20 (7.7)	5 (1.9)	0	0
	Mur 5	245	21 (8.6)	18 (7.3)	3 (1.2)	0	0
	Mur 10	249	62 (24.9)	41 (16.5)	16 (6.4)	4 (1.6)	1 (0.4)
	Mur 20	239	95 (40.1)	56 (23.6)	30 (12.7)	9 (3.8)	0
	Pio 15	251	36 (14.3)	33 (13.1)	3 (1.2)	0	0
CV168018	Mur 2.5	111	9 (8.1)	7 (6.3)	2 (1.8)	0	0
	Mur 5	114	13 (11.4)	12 (10.5)	1 (0.9)	0	0
	Placebo	115	9 (7.8)	7 (6.1)	2 (1.7)	0	0
	Mur 5 OL	109	10 (9.2)	10 (9.2)	0	0	0
Monotherapy	Mur ≤ 5	965	93 (9.6)	76 (7.9)	17 (1.8)	0	0
CV168021	Mur 2.5+Gly	191	18 (9.4)	14 (7.3)	4 (2.1)	0	0
	Mur 5+Gly	193	19 (9.8)	16 (8.3)	3 (1.6)	0	0
	Placebo+Gly	199	14 (7.0)	13 (6.5)	1 (0.5)	0	0
CV168022	Mur 2.5+Met	233	22 (9.4)	17 (7.3)	5 (2.1)	0	0
	Mur 5+Met	205	32 (15.6)	27 (13.2)	4 (2.0)	1 (0.5)	0
	Placebo+Met	214	8 (3.7)	6 (2.8)	2 (0.9)	0	0
CV168025	Mur 5+Met	587	54 (9.2)	46 (7.8)	7 (1.2)	1 (0.2)	0
	Pio 30+Met	572	41 (7.2)	37 (6.5)	3 (0.5)	1 (0.2)	0
+ Metformin	All Mur 5 + Met	792	86 (10.9)	73 (9.2)	11 (1.4)	2 (0.3)	0

Table 7.3.B pools the results of the above studies by year of exposure in a similar fashion to the applicant’s presentation of congestive heart failure (please see Section 7.1). Although groups are not entirely comparable because of the presence or absence of

concomitant medications, Table 7.3.C demonstrates that the rate of edema in the muraglitazar ≤ 5 mg group approximates that of pioglitazone ≤ 45 mg, and both groups have rates greater than placebo. For unclear reasons, the pioglitazone 15 mg group had much higher incidence of edema than any of the muraglitazar doses ≤ 5 mg or the pioglitazone 30 mg + metformin group. This pattern remained when examining those subjects who were and were not rescued to pioglitazone 45 mg in study CV168006. However, it is noted (as discussed in Section 7.1) that none of the subjects in the pioglitazone 15 mg group in either the ST or LT phases of study CV168006 developed heart failure.

		MUR 1.5	MUR 2.5	MUR 5	PLA	PIO 15	PIO 30
CV168018	Incidence Yrs of Exposure Subjects/100 Yrs		9/111 46.60 19.31	13/114 48.04 27.06	9/115 43.84 20.53		
CV168021	Incidence Yrs of Exposure Subjects/100 Yrs		18/191 79.04 22.77	19/193 83.68 22.71	14/199 77.91 17.97		
CV168022	Incidence Yrs of Exposure Subjects/100 Yrs		22/233 98.28 22.39	33/205 87.27 37.81	8/214 82.43 9.71		
CV168025	Incidence Yrs of Exposure Subjects/100 Yrs			54/587 251.35 21.48			41/572 239.89 17.09
CV168006 ST	Incidence Yrs of Exposure Subjects/100 Yrs	25/259 86.96 28.75		21/245 92.05 22.81		36/251 82.90 43.43	
Total	Incidence % Yrs of Exposure Subjects/100 Yrs	25/259 9.7% 86.96 28.75	49/535 9.2% 223.92 21.88	140/1344 10.4% 562.39 24.89	31/528 5.9% 204.18 15.18	36/251 14.3% 82.90 43.43	41/572 7.2% 239.71 17.10

	MUR ≤ 5 mg*	Placebo	PIO ≤ 45 mg†
	N = 2138	N = 528	N = 823
Subjects with Edema AE (%)	239 (10.1)	31 (5.9)	77 (9.4)
Years of Exposure	946.57	204.18	322.61
Subjects/100 Years	25.25	15.18	23.87

* Includes MUR 0.5 mg for consistency with the applicant's pooling method

† This pioglitazone group had no glyburide add-on therapy; however, events in the muraglitazar + glyburide were not substantially different than in the monotherapy and combination with metformin studies. Furthermore, rates in the placebo monotherapy and + glyburide studies were similar.

Long Term

Table 7.3.D (LT phase of study CV168006) demonstrates that a similar percentage of subjects in the muraglitazar ≤ 5 mg reported edema-related AEs to the pioglitazone-treated subjects (with a slightly higher incidence of moderate intensity events in the muraglitazar groups than the pioglitazone group), and that the cumulative incidence of

edema over the 104-week period was higher for both muraglitazar and pioglitazone than that during the ST phase.

Table 7.3.D. Number (%) of Subjects with Edema-related AEs, Total and by Intensity, CV168006LT							
Regimen	Dose (mg)	Started LT (N)	Subjects with Edema AE (%)	Edema Adverse Events by Treatment Group and Highest Severity			
				Mild	Moderate	Severe	Very Severe
Non-Titrated	Mur 1.5	75	14 (18.7)	9 (12.0)	5 (6.7)	0	0
	Mur 5	108	27 (25.0)	20 (18.5)	7 (6.5)	0	0
	Mur 10	156	75 (48.1)	44 (28.2)	26 (16.7)	5 (3.2)	0
	Mur 20	75	42 (56.0)	23 (30.7)	13 (17.3)	6 (8.0)	0
	Pio 15	65	20 (30.8)	17 (26.2)	3 (4.6)	0	0
By Maximum Dose	Mur 1.5	121	24 (19.8)	15 (12.4)	9 (7.4)	0	0
	Mur 5	206	58 (28.2)	39 (18.9)	18 (8.7)	1 (0.5)	0
	Mur 10	274	107 (39.1)	68 (24.8)	33 (12.0)	6 (2.2)	0
	Mur 20	238	108 (45.4)	65 (27.3)	33 (13.9)	10 (4.2)	0
	Pio 15	64	19 (29.7)	16 (25.0)	3 (4.7)	0	0
	Pio 45	82	17 (20.7)	13 (15.9)	3 (3.7)	1 (1.2)	0

Figures 7.3.A and 7.3.B present the time to the first edema-related event using Kaplan-Meier curves in the LT monotherapy study CV168006.

Figure 7.3.A. Time to First Edema-related AE - Kaplan-Meier Curve, LT Monotherapy Non-titrated Dose (CV168006)

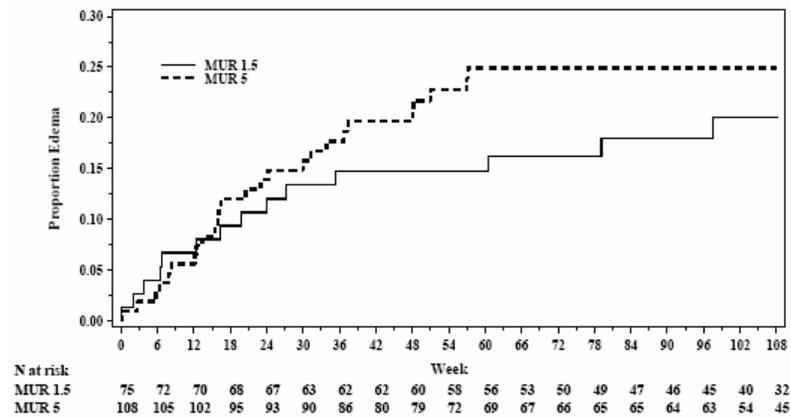
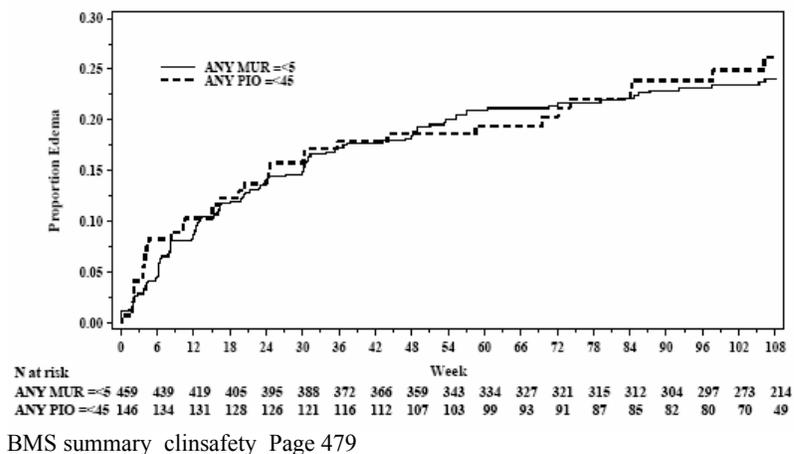


Figure 7.3.B. Time to First Edema-related AE - Kaplan-Meier Curve, LT Monotherapy Initial or Titrated Dose (CV168006)



In summary, the incidence of edema in muraglitazar-treated subjects was greater than those on placebo, occurred in a dose-related fashion (with rates dramatically increasing at muraglitazar 10 and 20 mg), and increased with drug exposure. Subjects in the muraglitazar ≤ 5 mg group generally had similar rates of events to those in the pioglitazone ≤ 45 mg group. In these doses, edema-related events were generally of mild or moderate severity. The only two SAEs of edema-related events in the clinical program occurred in subjects on muraglitazar 20 mg.

7.4 Hypoglycemia

In the clinical pharmacology studies, there were no episodes of hypoglycemia in either the normoglycemic non-diabetic or hyperglycemic diabetic subjects who received muraglitazar at doses up to 20 to 50 mg daily for one month.

In the Phase 2 and 3 type 2 diabetes studies, reported hypoglycemia events were identified by the following Preferred Terms: *hypoglycaemia*, *blood glucose decreased*, or *blood glucose abnormal*. Confirmed hypoglycemia was defined as any event with symptoms consistent with hypoglycemia (sweating, shakiness, increased heart rate, hunger, confusion, dizziness/lightheadedness, and other), and confirmed by a fingerstick blood glucose reading of ≤ 50 mg/dL.

There were three SAEs of hypoglycemia in the short term Phase 2 and 3 studies; all reported by a single investigator in study CV168021: two subjects on muraglitazar 2.5 mg + glyburide and one subject on muraglitazar 5 mg + glyburide. All received outpatient, intravenous glucose treatment. Two additional subjects had an event of hypoglycemia requiring medical intervention, one receiving muraglitazar 2.5 mg + glyburide; one receiving placebo + glyburide.

Table 7.4.A illustrates the rates of reported and confirmed hypoglycemia events in the short term phases of the Phase 2 and 3 studies.

Table 7.4.A. Number (%) of Subjects with Hypoglycemia-related AEs, Reported and Confirmed, ST Type 2 Diabetes Studies						
Study	Dose (mg)	N	Reported Hypoglycemia		Confirmed Hypoglycemia	
			Events	Subjects (%)	Events	Subjects (%)
CV168006ST	Mur 0.5	236	35	18 (7.6)	0	0
	Mur 1.5	259	32	20 (7.7)	0	0
	Mur 5	245	70	33 (13.5)	2	2 (0.8)
	Mur 10	249	71	38 (15.3)	2	2 (0.8)
	Mur 20	239	71	39 (16.5)	3	3 (1.3)
	Pio 15	251	28	20 (8.0)	0	0
CV168018	Mur 2.5	111	0	0	0	0
	Mur 5	114	3	3 (2.6)	0	0
	Placebo	115	2	2 (1.7)	0	0
	Mur 5 OL	109	2	2 (1.8)	0	0
Monotherapy	Mur ≤ 5	965	140	74 (7.7)	2	2 (0.2)
CV168021	Mur 2.5+Gly	191	57	28 (14.7)	19	14 (7.3)
	Mur 5+Gly	193	86	37 (19.2)	28	20 (10.4)
	Placebo+Gly	199	32	16 (8.0)	20	10 (5.0)
CV168022	Mur 2.5+Met	233	11	7 (3.0)	0	0
	Mur 5+Met	205	5	5 (2.4)	0	0
	Placebo+Met	214	12	4 (1.9)	9	1 (0.5)
CV168025	Mur 5+Met	587	28	17 (2.9)	3	3 (0.5)
	Pio 30+Met	572	12	9 (1.6)	1	1 (0.2)
+ Metformin	All Mur 5 + Met	792	33	22 (2.8)	3	3 (0.4)
CV168006LT	Any Mur ≤ 5	459	182	86 (18.7)	6	5 (1.1)
	Any Pio ≤ 45	146	27	18 (12.3)	2	2 (1.4)

Several observations can be drawn from the above:

- Reporting rates of hypoglycemia for the monotherapy studies varied widely between studies; it appears that hypoglycemia symptoms were elicited by the investigator at each visit in study CV168006, and only reported when the subject volunteered information in study CV168018. Even so, when muraglitazar ≤ 5 mg is pooled across monotherapy in the short term, the rates of reported hypoglycemia are comparable to pioglitazone ≤ 45 mg (7.7% versus 8.0%, respectively).
- The addition of metformin to muraglitazar did not increase the risk of reported or confirmed hypoglycemia as compared to monotherapy.
- The addition of glyburide increased the risk of reported and confirmed hypoglycemia, and the risk was higher in muraglitazar-treated subjects than placebo.
- Rates of confirmed hypoglycemia were generally low, with the exception of the glyburide add-on study.
- Rates of confirmed hypoglycemia increased in the LT study CV168006 as compared to the ST reflecting increased exposure.

There was one subject with an SAE of hypoglycemia in the long term phase of study CV168006 (monotherapy), in a subject randomized to muraglitazar 10 mg. On Day 600, the subject had symptoms of hypoglycemia after an unusual amount of walking and went to the emergency room, where her blood glucose was assessed as 52 mg/dL. She was treated with 4 ampules of IV glucose with resolution of her symptoms and released. No action was taken with regards to study drug.

7.5 Body Weight

The body weight gain seen with PPAR- γ agonism is likely due to several mechanisms. As discussed above in the subsection on edema, fluid retention is a common finding and may cause weight gain. Additionally, because PPAR- γ agonists increase pathways involved in energy storage and stimulate adipocyte differentiation, increased fat accumulation is a possibility with these compounds. Furthermore, improved diabetic control and decreased glucosuria may lead to retention of calories and weight gain. Muraglitazar, having PPAR- α activity in addition to - γ , theoretically could offset this adipogenic property.⁴ In animals, PPAR- α agonists have been shown to regulate genes in the liver to stimulate mitochondrial and peroxisomal fatty acid oxidation and induce uncoupling proteins in muscle resulting in increased thermogenesis;⁵ however, this thermogenic effect has not been demonstrated with fibrate (PPAR- α) therapy in humans.

Weight gain was a common adverse event in the muraglitazar-treated groups as would be expected, and was the most common adverse event leading to discontinuation in doses proposed for marketing. There is evidence that the use of antihyperglycemic medications concomitantly with PPAR- γ compounds leads to a greater amount of weight gain. Therefore, Table 7.5.A demonstrates the weight gain-related total adverse events and those leading to discontinuation by treatment randomization and concomitant antihyperglycemic medication. In addition, last observation carried forward (LOCF) mean change in weight over the short term phase (24 weeks) is presented.

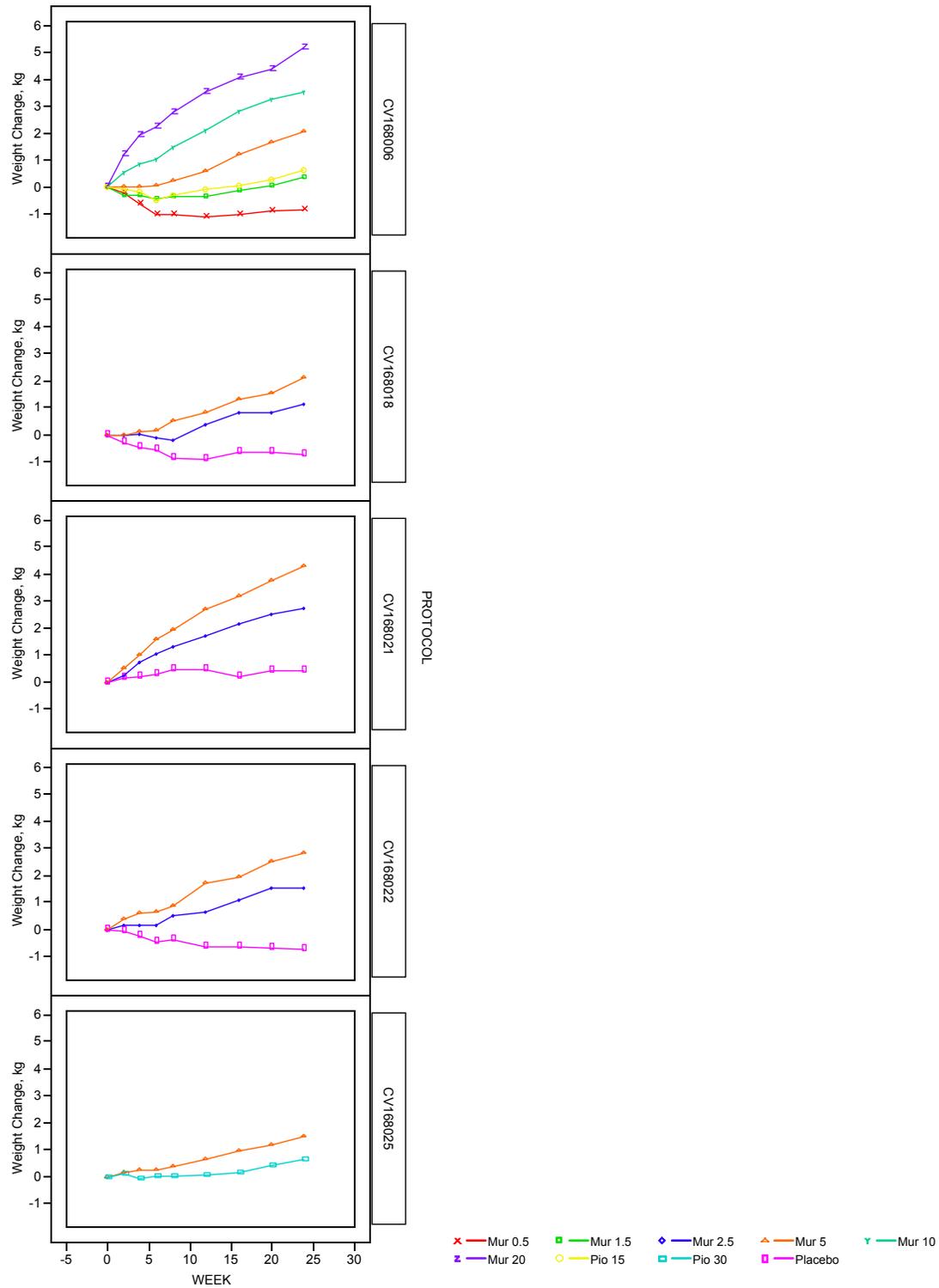
4 Carmona MC, et al. Fenofibrate Prevents Rosiglitazone-Induced Body Weight Gain in ob/ob Mice. *International Journal of Obesity* 2005 29: 864–871.

5 Torra IP, et al. Peroxisome Proliferator-Activated Receptor Alpha in Metabolic Disease, Inflammation, Atherosclerosis, and Aging. *Curr Opin Lipidology* 1999 10: 151-199.

Table 7.5.A. Number (%) of Subjects with Weight Gain AEs and LOCF Mean Weight Change, ST Type 2 Diabetes Studies						
Study	Dose (mg)	Subjects with AE of Weight Increased, (%)			Weight Change LOCF, at Week 24	
		N	Total	Leading to discontinuation	N	Mean Change, kg (95% CI)
CV168006	Mur 0.5	236	1 (0.4)	0	231	-1.13 (-1.62, -0.63)
	Mur 1.5	259	1 (0.4)	0	259	-0.22 (-0.69, 0.26)
	Mur 5	245	13 (5.3)	3 (1.2)	245	1.60 (1.11, 2.10)
	Mur 10	249	20 (8.0)	4 (1.6)	249	3.19 (2.71, 3.67)
	Mur 20	239	39 (16.5)	7 (2.9)	237	4.85 (4.36, 5.34)
	Pio 15	251	7 (2.8)	0	251	0.19 (-0.28, 0.66)
CV168018	Mur 2.5	111	3 (2.7)	0	111	1.05 (0.40, 1.71)
	Mur 5	114	2 (1.8)	0	112	2.10 (1.45, 2.75)
	Placebo	115	0	0	114	-0.78 (-1.43, -0.14)
	Mur 5 OL	109	2 (1.8)	0	106	2.90 (2.14, 3.66)
CV168021	Mur 2.5+Gly	191	5 (2.6)	1 (0.5)	183	2.63 (2.16, 3.09)
	Mur 5+Gly	193	13 (6.7)	1 (0.5)	191	4.06 (3.61, 4.52)
	Placebo+Gly	199	4 (2.0)	0	197	0.43 (-0.02, 0.88)
CV168022	Mur 2.5+Met	233	5 (2.1)	0	229	1.40 (0.99, 1.80)
	Mur 5+Met	205	9 (4.4)	1 (0.5)	202	2.76 (2.33, 3.18)
	Placebo+Met	214	0	0	212	-0.73 (-1.14, -0.31)
CV168025	Mur 5+Met	587	15 (2.6)	0	576	1.39 (1.11, 1.68)
	Pio 30+Met	572	2 (0.3)	0	567	0.56 (0.27, 0.84)

Figure 7.5.A graphically demonstrates the change in weight in subjects over the course of the ST phase by treatment group; the effect is dose-and time-related.

Figure 7.5.A. Weight Change (kg) by Treatment Group, ST phase



There is no evidence from the above data that the addition of PPAR- α agonism to - γ with muraglitazar mitigates the weight gain effect typically seen with PPAR- γ compounds. Given the morbidity associated with obesity in the type 2 diabetic population, significant increases of body weight may limit the use of this drug.

7.6 Microscopic Hematuria/Bladder Cancer

Preclinical testing has demonstrated transitional cell urinary bladder tumors in male rats at exposures relevant to humans at the proposed clinical doses. Therefore, a safety monitoring plan was established in the muraglitazar Phase 3 clinical program for the active screening of microscopic hematuria (defined as ≥ 2 -5 RBCs per high-power field). Subjects who had two of three urinalyses positive for microscopic hematuria were to be referred to a urologist for consultation.

The applicant pooled those cases for subjects who received muraglitazar for up to 24 weeks either as monotherapy or as combination therapy, and only in those subjects randomized to muraglitazar ≤ 5 mg. Table 7.6.A demonstrates that the incidence of microscopic hematuria (MH) was comparable for all three treatment groups. The incidence of MH for those without an identified cause (total subjects minus common cause identified) was 3.9%, muraglitazar; 2.7%, placebo; and 3.4%, pioglitazone.

Table 7.6.A. Number (%) of Subjects with Microscopic Hematuria, MUR up to 5 mg Pooled (ST Phase)						
	Any MUR ≤ 5		Any PLA		Any PIO ≤ 45	
	N = 1634		N = 528		N = 572	
Total Subjects With Microscopic Hematuria	163	(10.0)	42	(8.0)	53	(9.3)
Total Subjects With MH And Common Cause Identified N (%)	100	(6.1)	28	(5.3)	34	(5.9)
Menses	27	(1.7)	2	(0.4)	4	(0.7)
Kidney Stones	5	(0.3)	2	(0.4)	2	(0.3)
Vigorous Exercise	11	(0.7)	4	(0.8)	5	(0.9)
Urinary Tract Infection	44	(2.7)	11	(2.1)	17	(3.0)
Sexual Activity	11	(0.7)	5	(0.9)	3	(0.5)
Trauma	3	(0.2)	0		0	
Other	13	(0.8)	6	(1.1)	5	(0.9)
Total Subjects With MH And Action Taken N (%)	155	(9.5)	40	(7.6)	51	(8.9)
Treatment With Antibiotic	40	(2.4)	10	(1.9)	18	(3.1)
Follow-Up Urinalysis	136	(8.3)	35	(6.6)	46	(8.0)
Referral To Urologist	25	(1.5)	11	(2.1)	5	(0.9)
Study Discontinuation	2	(0.1)	1	(0.2)	2	(0.3)
Other	11	(0.7)	4	(0.8)	3	(0.5)

BMS summary_clinsafety Page 597

Follow-up information requested from the applicant regarding urologist findings revealed that there was a total of 95 subjects (of all subjects in the clinical program including safety updates), who were evaluated for microscopic hematuria. The majority of these evaluations were normal. Other common findings included nephrolithiasis, urinary tract

infection, and prostate disease. Two cases of bladder cancer (one in a muraglitazar-treated subject and one in a pioglitazone-treated subject) were discovered; of note, there were two additional cases of bladder cancer (one muraglitazar and one pioglitazone) diagnosed during the study (please see Table 7.6.B, below). The applicant did not provide specific information on microscopic hematuria from the LT phases of the studies.

Table 7.6.B lists the five subjects who developed new-onset or recurrent bladder cancer during the course of the study. The small number of subjects with bladder cancer precludes one from drawing any meaningful conclusions.

Subject ID	Days on Drug	Treatment Group	Preferred Term
CV168006-336-6	58	MUR 10	Bladder Cancer*
CV168006-226-9	573	MUR 10	Bladder Cancer
CV168006-265-4	256	PIO 15	Bladder Cancer Recurrent
CV168025-123-4	170	PIO 30	Bladder Cancer

* This was identified as a recurrence of previous bladder cancer (1976).

7.7 Other Malignant Neoplasms

Because compounds with PPAR- γ activity have been demonstrated to be multi-species, multi-strain, multi-site carcinogens in animals (and are therefore classified as ‘probable human carcinogens’), careful attention has been paid to any preclinical carcinogenicity potential of this drug. Therefore, the clinical studies have also been examined for any possible safety signal with regards to cancer.

In the Phase 2 and 3 studies, the incidence of and death due to malignant neoplasm was higher for muraglitazar and pioglitazone than placebo. Table 7.7.A from the applicant’s pharmacovigilance plan submitted July 5, 2005, summarizes the rate of malignant neoplasms in the Phase 2 and 3 clinical program (events were only included from the time of the original NDA filing). This table demonstrates that although muraglitazar-treated subjects had a higher incidence of malignant neoplasm than placebo- or pioglitazone-treated subjects, the incidence in patient-years is similar between muraglitazar- and pioglitazone-treated subjects. There does not appear to be a particular tumor type or organ affected identified for concern.

Table 7.7.A. Summary of Malignant Neoplasms in Phase 2 and Phase 3 Muraglitazar Clinical Trials (including CV168006LT and CV168008)			
Subtypes of Malignant Neoplasms	Number of Events		
	Any Muraglitazar n = 3226	Any Pioglitazone n = 823	Placebo n = 591
Bladder cancer	2a,b	1b	0
Non-melanotic skin cancer	5	1	0
Leukaemias	1	0	1
Brain neoplasm	1	0	0
Breast cancer	3b, c	0	0
Endometrial cancer	2c	0	0
Lung neoplasm malignant	2	0	0
Malignant melanoma	2	0	0
Oesophageal cancer	3	0	0
Pancreatic cancer	2	0	0
Prostate cancer	3a	2	1
Throat cancer	0	1	0
Total Number of Events	26	5	2
Total Number of patients	24 (0.74%)	5 (0.61%)	2 (0.34%)
Patient Years of Exposure	2648.1	522.54	281.41
Incidence per 1000 patient-years exposure	9.06	9.57	7.11

Source: Summary of Clinical Safety Appendix 2.3.7B
Note: includes all reported malignant neoplasms up to 30 days post-ST phase (but prior to LT phase if any) for Studies CV168018, CV168021, CV168022 and CV168025; from the ST + LT phase collected up to June 14, 2004 for Study CV168006; and the ST +LT phase for Study CV168008.
Note: includes both serious and non-serious adverse events
Note: total patient years of exposure = the duration of treatment up to the date of the first cancer event, if applicable
a Includes one patient for whom prostate cancer and bladder cancer were reported
b Neoplasm recurrence in one subject
c Includes one patient for whom breast cancer and endometrial cancer were reported

BMS pharmacovigilance_plan, Page 25

As the applicant notes, of the 26 malignant neoplasms in the muraglitazar group:

- Twelve were reported within three months of the initiation of study drug treatment
- Five were reported within six months of the initiation of study drug treatment
- Two were reported within one year of the initiation of study drug treatment
- Seven were reported after one year of the initiation of study drug treatment, but < 2 years of study drug exposure.

Seven new malignant neoplasms were reported in the 120-day Safety Update (two in Study CV168006, three in Study CV168021, and two in Study CV168022; not reported in Table 7.7.A), all in muraglitazar-treated subjects:

- One skin basal cell carcinoma in Subject CV168021-305-2, receiving muraglitazar 2.5 mg + glyburide 15 mg
- One hepatocellular carcinoma in Subject CV168022-250-15 on muraglitazar 2.5 mg + metformin 1500 mg
- One metastatic lung cancer in Subject CV168006-80-9 on muraglitazar 5 mg
- One malignant melanoma in Subject CV168021-256-1 on muraglitazar 5 mg + glyburide 15 mg

- One prostate cancer in Subject CV168006-23-10 on muraglitazar 1.5 mg
- Two metastatic small cell lung cancers in Subject CV168021-258-1 on muraglitazar 2.5 mg + glyburide 15 mg, and CV168022-142-4 on muraglitazar 5 mg + metformin 2000 mg

Of these subjects, three are known to have died (CV168006-80-9, CV168022-142-4, and CV168022-250-15).

7.8 Hematologic Findings

PPAR- γ compounds are associated with a decrease in hematologic parameters, due to hemodilution because of fluid retention, as well as potentially increased bone marrow fat because of PPAR-activated preadipocyte differentiation and suppression of red blood cell production. Table 7.8.A demonstrates the number (%) of subjects at doses of muraglitazar up to 5 mg who developed abnormal hematological values during the ST phase of the Phase 2 and 3 studies. The incidence of decreased values was low in all groups, but appears to be dose-dependent and possibly greater than placebo or pioglitazone.

Table 7.8.A. Number (%) of Subjects with Marked Abnormalities for Hematology Labs, Muraglitazar up to 5 mg, ST Phase									
	Non-titrated Dose								
	MUR 1.5			Any MUR 2.5			Any MUR 5		
	N	Low (%)	High (%)	N	Low (%)	High (%)	N	Low (%)	High (%)
Hemoglobin	174	0	NE	522	0	NE	1275	1 (0.1)	NE
Hematocrit	173	0	NE	521	3 (0.6)	NE	1268	9 (0.7)	NE
Leukocytes	174	0	NE	522	0	NE	1275	0	NE
	Initial or Titrated Dose								
	Any MUR \leq 5			Any PLA			Any PIO \leq 45		
	N	Low (%)	High (%)	N	Low (%)	High (%)	N	Low (%)	High (%)
Hemoglobin	2334	1 (0.0)	NE	520	0	NE	811	0	NE
Hematocrit	2324	12 (0.5)	NE	513	1 (0.2)	NE	807	0	NE
Leukocytes	2334	0	NE	520	0	NE	811	0	NE

N = number of Treated Subjects with baseline value and at least one value during ST; NE = not evaluated

BMS summary_clinsafety, Page 109

Table 7.8.B demonstrates the mean changes at Week 104 of the listed hematologic variables. Muraglitazar-treated subjects appear to have slightly greater decreases of these values than pioglitazone-treated subjects.

Table 7.8.B. Mean (SD) Change from Baseline in Laboratory Tests at Week 104, LT Monotherapy		
Parameter	Initial or Titrated	
	Any Mur \leq 5 N = 283	Any Pio \leq 45 N = 88
Hemoglobin (g/dL)	-0.35 (0.89)	-0.31 (0.82)
Hematocrit (%)	-0.86 (2.68)	-0.69 (2.36)
Leukocytes (x 10 ³ cells/ μ L)	-0.28 (1.34)	-0.19 (1.79)
ANC (x 10 ³ cells/ μ L)	-0.30 (1.16)	-0.19 (1.66)

BMS summary_clinsafety, Page 110

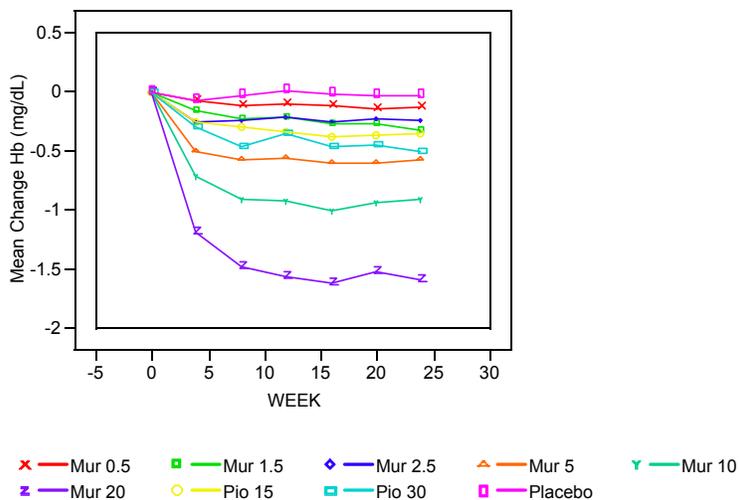
This reviewer searched the database for adverse events of Preferred Terms aplastic anemia, pancytopenia, or agranulocytosis. No subject in the clinical program developed these adverse events in any of the treatment groups. Thrombocytopenia was seen infrequently.

7.8.1 Anemia

In subjects with type 2 diabetes, the incidence of adverse events of anemia for in subjects receiving muraglitazar up to 5 mg (0.6%, 1 SAE), placebo (0.4%), and pioglitazone (0.6%, 1 SAE) was comparable. There were four discontinuations due to anemia reported in the original NDA submission (ST phase): one in the muraglitazar 20 mg group, two in the muraglitazar 5 mg group (one SAE), and one in the muraglitazar 5 mg OL group. As shown above in Table 7.8.A, slightly more subjects in the muraglitazar-treated group developed low hematocrit during the study than those randomized to placebo or pioglitazone. One subject (muraglitazar 5 mg + metformin) developed hemoglobin < 8 g/dL (7.7 g/dL; baseline = 14.9 g/dL) starting on Day 29, with study discontinuation on Day 33. Severe peripheral and facial edema were reported on Day 34. The subject also had an adverse event of leukopenia (Day 34, WBC = 3700 cells/ μ L; baseline = 3900 cells/ μ L). According to the case report form, both the anemia and leukopenia resolved after study discontinuation (Day 78).

Figure 7.8.1.A demonstrates the dose-relationship of hemoglobin in the Phase 2 and 3 studies combined, ST phase. The changes in hemoglobin at the muraglitazar doses proposed for marketing are comparable to that of pioglitazone. Decreases in hemoglobin appear to plateau by Week 8.

Figure 7.8.1.A. Mean Change in Hemoglobin by Week, Short Term Type 2 Diabetes Studies



In subjects on LT monotherapy, the incidence of anemia for subjects on muraglitazar up to 5 mg (0.7%) was lower than that for pioglitazone (2.7%). There were no SAEs of

anemia reported, although four subjects discontinued due to anemia, all in the muraglitazar 20 mg group.

7.8.2 Neutropenia

Table 7.8.2.A demonstrates the number (%) of subjects with adverse events of Preferred Term *neutropenia* or *neutrophil count decreased*, across all clinical ST studies (including CV168008). The incidence of neutropenia adverse events increases at doses of muraglitazar 10 mg and above. As seen below, there does not appear to be a dose-related increase in the incidence of these adverse events at doses of muraglitazar \leq 5 mg.

Table 7.8.2.A. Decreased ANC-Related AEs by Muraglitazar Dose, ST Phase*								
	Mur 0.5 N = 236	Mur 1.5 N = 259	Mur 2.5 N = 535	Mur 5 N = 1517	Mur 10 N = 310	Mur 20 N = 369	All Pio N = 823	All Pla N = 591
Total Subjects	1 (0.4)	3 (1.2)	2 (0.4)	4 (0.3)	8 (2.6)	9 (2.4)	1 (0.1)	1 (0.2)
Neutropenia	1 (0.4)	1 (0.4)	1 (0.2)	4 (0.3)	2 (0.6)	6 (1.6)	0 (0.0)	1 (0.2)
Neutrophil Count Decreased	0 (0.0)	2 (0.8)	1 (0.2)	0 (0.0)	6 (1.9)	3 (0.8)	1 (0.1)	0 (0.0)

* Includes study CV168008

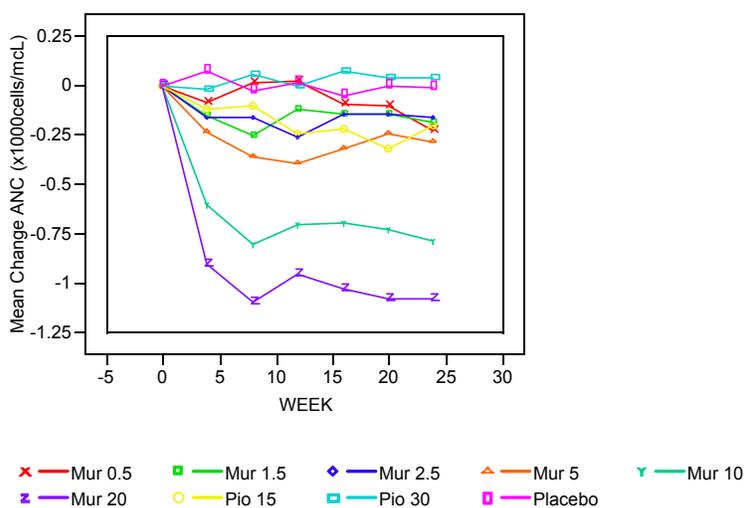
Three of these events were coded as SAEs, one in the muraglitazar 1.5 mg and two in the muraglitazar 20 mg groups:

- Subject CV168006-196-21 (muraglitazar 20 mg) was a 54 year-old white female who experienced neutropenia after 121 days of treatment. Her absolute neutrophil count of was 900 cells/dL on Day 121 (baseline 3,140 cells/dL). Of note, she was also diagnosed with unstable angina on Day 121 and arterial stenosis on Day 126 and was discontinued from the study. The subject was hospitalized for a cardiac catheterization that revealed coronary blockages requiring coronary artery bypass surgery.
- Subject CV168006-197-9 (muraglitazar 1.5 mg) was 64 year-old white female who experienced neutropenia after 124 days of treatment. On the day of randomization, her ANC was 3762 cells/dL. Two days prior on Day 122, the subject presented to her family doctor complaining of micturition and urethral area discomfort. She was diagnosed with cystitis and prescribed trimethoprim for 3 days. On Day 124, the ANC was 286 cells/dL. Study medication was discontinued on Day 126. The ANC was 3740 cells/dL seven days after study drug was discontinued. Although the investigator considered the event as probably related to study drug, he suggested that trimethoprim possibly induced the neutropenia.
- Subject CV168008-16-1 (muraglitazar 20 mg) was a 62 year old white female who experienced an important medical event of neutropenia and was discontinued from study medication after 29 days of treatment. At the time of discontinuation the subject experienced mild depression and facial periorbital edema and her neutrophil count was 970 cells/uL (baseline 2,106 cells/uL). Study medication was discontinued and no treatment was given. After three days the neutrophil count returned to within normal limits 1,522 cells/uL and after 15 days increased to 1697 cells/uL. The event resolved after 15 days.

Thirteen subjects were reported discontinued due to AEs of *neutropenia* or *neutrophil count decreased*: one muraglitazar 0.5 mg, two muraglitazar 1.5 mg, two muraglitazar 5 mg, four muraglitazar 10 mg, and four muraglitazar 20 mg. Ten (77%) of these events occurred in the ST phase.

Figure 7.8.2.A demonstrates the dose-relationship of absolute neutrophil count (ANC) in the Phase 2 and 3 studies combined, ST phase. ANC decreases are greater in the muraglitazar-treated groups than either pioglitazone- or placebo-treated groups. Decreases in ANC appear to plateau by Week 8.

Figure 7.8.2.A. Mean Change in ANC by Week, Short Term Type 2 Diabetes Studies



The applicant considered subjects who had ANC < 1000 cells/ μ L on two consecutive visits as having clinically significant marked laboratory analyses; three subjects randomized to muraglitazar \leq 5 mg and one placebo-treated subject met this criterion during the ST or LT phase of the clinical program:

- Subject CV168025-289-71 (muraglitazar 5 mg plus metformin, ST phase) had an absolute neutrophil count close to 1000 cells/ μ L at baseline (1056 cells/ μ L). The ANC returned to normal four days after treatment interruption and remained within normal limits after four additional months of muraglitazar treatment.
- Subject CV168021-192-6 (placebo, ST phase) had normal levels at the beginning of the study (2662 cells/ μ L) and had an ANC < 1000 cells/ μ L on three occasions during the study (136 cells/ μ L on Day 27, 170 cells/ μ L on Day 81, and 392 cells/ μ L on Day 104).
- Subject CV168006-140-9 (muraglitazar 1.5 mg, LT phase) had ANC counts close to 1000 cells/ μ L at baseline (1125 cells/ μ L).
- Subject CV168006-233-8 (muraglitazar 5 mg, LT phase) had variable levels within the normal range throughout the study, and had two consecutive low counts on Days 751 (400 cells/ μ L) and 758 (593 cells/ μ L) of the study.

Blinded bone marrow biopsies were obtained from two patients with ANC decreases (CV168006-422-2: the biopsy was performed four days after the subject discontinued muraglitazar 10 mg, and CV168021-301-17: the biopsy was performed while the subject was on placebo), which both revealed moderately decreased cellularity suggestive of an early maturation delay. This bone marrow effect in these two cases appeared to be reversible (by clinical examination and laboratory results) upon discontinuation of study drug.

7.9 Cholelithiasis

Clinical experience with PPAR- α agonists (fibrates) has suggested an increased risk of cholelithiasis due to alterations in biliary lipid composition.⁶ In the Phase 2 and 3 studies, the incidence of cholelithiasis was low (< 1%) following the administration of muraglitazar as ST or LT therapy. In subjects with type 2 diabetes, the incidence of cholelithiasis for muraglitazar \leq 5 mg, placebo, and pioglitazone \leq 45 mg was comparable (7 of 2374; 0.3%, 2 of 528; 0.4%, and 2 of 823; 0.2%, respectively) during the ST phase. During the LT phase, the incidence of cholelithiasis for muraglitazar \leq 5 mg and pioglitazone \leq 45 mg was comparable (4 of 459; 0.9% versus 1 of 146; 0.7%).

Five subjects had SAEs of cholelithiasis or cholecystitis in the ST phase: one subject on muraglitazar 1.5 mg, two subjects on muraglitazar 5 mg, one subject on muraglitazar 10 mg, and one subject on placebo. One subject on muraglitazar 5 mg required no treatment; the rest underwent cholecystectomy with rapid recovery.

Two subjects had important medical events of elevated LFTs and gallstones. Please see Section 7.10 (Liver Findings) for narratives of these events.

7.10 Liver Findings

Clinical Pharmacology

There was one discontinuation due to elevated liver enzymes (\sim 8 x ULN) in the clinical pharmacology studies. Subject CV168046-1-23, a 20 year-old healthy white Hispanic male on no concomitant medications was discontinued due to an adverse event of asymptomatic elevated serum hepatic transaminases one day after administration of seven doses of muraglitazar 10 mg (Phase 2, P2). A week prior, he had been administered seven doses of fenofibrate 160 mg (Phase 1, P1). His alanine aminotransferase (ALT) values during the study are provided in Table 6.10.A. This subject was discontinued due to these elevations in ALT, AST, and LDH. Unfortunately, the abnormalities were not followed further and resolution cannot be assured (they were still elevated after seven days off study drug). In the absence of data suggesting otherwise, this reviewer assumes that the subject experienced a drug-related hepatotoxic reaction.

6 Post MP, et al. Fibrates Suppress Bile Acid Synthesis via Peroxisome Proliferator-Activated Receptor- α -Mediated Downregulation of Cholesterol 7 α -Hydroxylase and Sterol 27-Hydroxylase Expression. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2001 21:1840

Table 7.10.A

Days	Visit	ALT (U/L)	AST (U/L)	LDH (U/L)	T. Bili (mg/dL)	ALP (U/L)
-14	SCREEN	34				
-1	P1 Day-1	38				
8	P1 Day 8	28	22	104	1.0	72
14	P2 Day-1	76				
22	P2 Day 8	353	161	318	1.1	85
28	P3 Day-1	385	121			
28	P3 Day-1	349	120	256		
29	DISCHRG	351	131	267	1.3	116
29	DISCHRG	378	136	290		

Note: P1 = fenofibrate phase; P2 = muraglitazar phase; the subject did not receive any medication in P3

Phase 2 and 3

Tables 7.10.B and 7.10.C demonstrate the incidence of elevated liver function tests in subjects on doses of muraglitazar ≤ 5 mg, ST and LT phases, respectively:

Table 7.10.B. Number (%) of Subjects with Liver Function Test Abnormalities During ST Phase, Muraglitazar up to 5 mg						
	Non-titrated Dose			Initial or Titrated Dose		
	Mur 1.5	Any Mur 2.5	Any Mur 5	Any Mur ≤ 5	Any Pla	Any Pio ≤ 45
	N= 177	N= 535	N=1296	N=2374	N= 528	N= 823
ALT (U/L)	n = 174	n = 512	n = 1266	n = 2315	n = 502	n = 806
ALT > 3*ULN	0 (0.0)	3 (0.6)	1 (0.1)	6 (0.3)	5 (1.0)	5 (0.6)
ALT > 5*ULN	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	1 (0.2)	3 (0.4)
ALT > 8*ULN	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	1 (0.2)	1 (0.1)
ALT > 30*ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST (U/L)	n = 174	n = 512	n = 1266	n = 2315	n = 503	n = 806
AST > 3*ULN	0 (0.0)	2 (0.4)	1 (0.1)	3 (0.1)	2 (0.4)	4 (0.5)
Total Bilirubin (mg/dL)	n = 174	n = 512	n = 1266	n = 2315	n = 502	n = 806
Bilirubin > 2 mg/dL	1 (0.6)	3 (0.6)	1 (0.1)	5 (0.2)	4 (0.8)	5 (0.6)
ALT (U/L) and Total Bilirubin (mg/dL)	n = 174	n = 512	n = 1266	n = 2315	n = 502	n = 806
ALT > 3*ULN and Bilirubin > 2 mg/dL	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)

BMS summary_clinsafety, Page 119

Table 7.10.C. Incidence of Liver Function Test Abnormalities, LT Monotherapy		
Parameter	Any Mur ≤ 5 N = 459	Any Pio ≤ 45 N = 146
ALT > 8 x ULN	0 (0)	0 (0)
ALT > 5 x ULN	0 (0)	1 (0.7)
ALT > 3 x ULN	3 (0.7)	1 (0.7)
AST > 3 x ULN	1 (0.2)	1 (0.7)
Total Bilirubin > 2 mg/dL	2 (0.4)	3 (2.1)
ALT > 3 x ULN and Total Bilirubin > 2 mg/dL	1 (0.2)	0 (0)

BMS summary_clinsafety, Page 120

These tables demonstrate that subjects on muraglitazar did not have an increased rate of markedly elevated LFTs as compared to those on either placebo or pioglitazone. The narrative of a subject randomized to muraglitazar 2.5 mg in the ST phase (Table 7.10.B) with ALT > 3x ULN (ALT ~ 16x ULN) and total bilirubin > 2 mg/dL is below, in addition to a subject (muraglitazar 1.5 mg) in the LT phase meeting this criterion (Table 7.10.C).

Subject CV168018-109-3 (muraglitazar 2.5 mg) was a 61 year-old white female, diagnosed with type 2 diabetes for two months prior to the study. Significant prior medical history included partial gastrectomy for duodenal ulcer, overweight, hypertension, asthma, mixed dyslipidemia, impaired fasting glucose, and prior tobacco use. On study Day 38, she experienced a non-serious adverse event of epigastric distress, described as mild in severity. She was treated with pantoprazole, scopolamine and an antacid. On study Day 42, she underwent an upper GI series procedure to determine the origin of the epigastric distress. On study Day 83 it was determined that she had gallstones, a non-serious adverse event of mild severity. She completed participation in the study on study Day 168. On Day 169, she had elevated liver enzymes (ALT ~ 16x ULN). She underwent a cholecystectomy on Day 176 and the event resolved on Day 183. The history of her LFTs throughout the study are provided in Table 7.10.D.

Table 7.10.D.

	ALT (U/L)	Bilirubin (mg/dL)	AST (U/L)	ALP (U/L)
Standard Range	2-34	0.1-1.2	11-35	45-140
Baseline/Screening	30	0.5	20	141
B00 (Day 0)	33	0.4	19	155
B04 (Day 57)	31	0.5	21	116
B07 (Day 113)	53	0.5	15	142
B99 (Day 168)	543	2.8	373	295
Post study	25	0.5	14	165
Post study	41	0.3	20	137

BMS cv168018, Page 1398

There was one subject who had the combination of ALT > 3x ULN and total bilirubin > 2 mg/dL during the long-term phase. Subject CV168006-252-4 (muraglitazar 1.5 mg) was a 65 year-old white Hispanic male, diagnosed with type 2 diabetes approximately one year prior to the study. Significant medical history included overweight, constipation, bladder stone, gallstones on ursodeoxycholic acid, chronic proton-pump therapy for gastritis, and alcohol use (two drinks on most days). On Day 324, the subject experienced abdominal pain, vomiting feverishness, chills and jaundice and liver echography was performed (results unavailable). The events resolved on study Day 326 and no treatment was given for the events. On Day 331, the subject had elevated liver function tests that showed an ALT of 152 U/L and total bilirubin of 2.4 mg/dL (Baseline ALT 18 U/L, baseline total bilirubin 0.8 mg/dL, see Table 7.10.E). Abdominal tomography and MRI revealed the presence of gallbladder stones and the investigator suggested that the symptoms and the abnormal elevated liver function tests might be acute cholangitis. A repeat test showed an ALT of 44 and total bilirubin of 1.0. He continued participation in the study.

Table 7.10.E.

Visit Day	ALT (U/L) Normal Range: 6-48 U/L	TBILI (mg/dL) Normal Range: 0.1-1.2 mg/dL
Day 1	18	0.8
Day 254	24	0.5
Day 331	152	2.4
Day 338	44	1.0

BMS cv168006lt, Page 3462

There was one SAE of liver cirrhosis in a 64 year old male in study CV168025 (muraglitazar 5 + metformin) with a history of hypertension, obesity, hypercholesterolemia, bowel perforation, arthritis, psoriasis, and alcohol (one drink on most days) and tobacco use. The subject was hospitalized on day 119 for suspicion of cancer due to weight loss and herpes zoster. An EGD demonstrated grade IV esophageal varices. On day 120 an abdominal ultrasound revealed an enlarged cirrhotic liver, splenomegaly, renal cysts, and a nodule in the region of the left kidney. A chest and abdominal CT scan on day 123 demonstrated questionable early cirrhotic changes in the liver, pancreatic head calcifications, ascites, and renal cysts. Liver function tests and hemoglobin/hematocrit remained normal. A final diagnosis of Child ‘A’ liver cirrhosis most probably of “dietary-toxin origin” (i.e., alcohol use or fatty liver) and esophageal varices was made. The subject was discontinued from the study on Day 130.

Subject CV168006-327-19 was a 52 year old white male who was hospitalized on Day 407 and ultimately discontinued from the study for an SAE of alcoholic hepatitis. The investigator reports that a history of alcohol abuse was discovered during the hospitalization. The hospitalization resulted in reported improvement of liver tests and general condition. Laboratory values upon admission (not included in database) were: total bilirubin 6.17 mg/dL, AST 224 U/L, ALT 110 U/L, GGT 4319 U/L, and triglyceride 4077 mg/dL. Liver function tests during the study are outlined in Table 7.10.F (Day 414 was post study discontinuation, and post SAE). According to the narrative, follow up LFTs on Day 456 were ALT 15 U/L, AST 16 U/L, and total bilirubin 0.7 U/L.

Table 7.10.F. Liver Function Tests by Day of Study, Subject CV168006-327-19

	-28	28	42	57	97	111	139	169	211	257	306	337	350	414 (post)
Albumin	4.2	4.3	4.2	4	4.1	4.2	4	4.2	4	4.1	4	4.1	3.8	3.4
Alk Phos	61	64	60	56	56	58	50	61	59	71	62	82	62	139
ALT	42	49	46	25	36	25	26	25	34	39	55	75	35	86
AST	32	50	38	21	34	21	19	26	25	33	54	121	35	57
T Bili	1.2	1.3	2	1.3	1.6	0.8	1.2	0.5	1.1	0.8	1.6	1.5	1.2	1.6

This reviewer also searched the database for subjects on doses of muraglitazar 10 and 20 mg who had ALT > 3x ULN. Two subjects on muraglitazar 10 mg in study CV168008 had an ALT > 3x ULN, with apparent resolution. Subject CV168008-53-21 had an ALT ~7x ULN, with elevated AST, but no elevation in total bilirubin. The abnormalities resolved the next week after the study drug was interrupted. He remained in the study (of note, he also had a separate incident of CK > 10x ULN later in the study associated with weight lifting, which also spontaneously resolved). These elevations were reported as an

adverse event. Subject CV168008-55-5 had an ALT ~9x ULN with total bilirubin 1.9 mg/dL and was diagnosed with gallstones. She underwent removal of the gallstone with resolution of the laboratory abnormalities.

As demonstrated in Table 7.10.G, there does not appear to be a significant difference in the overall rate of subjects with abnormal LFT-related adverse events between treatment groups. Furthermore, no subjects on muraglitazar were discontinued due to adverse events of elevated liver enzymes in the Phase 2 and 3 studies.

Preferred Term	All MUR N = 3226	All PIO N = 823	All PLA N = 591
Total Subjects	12 (0.4)	4 (0.5)	2 (0.3)
Alanine Aminotransferase Increased	8 (0.2)	0 (0.0)	0 (0.0)
Aspartate Aminotransferase Increased	5 (0.2)	0 (0.0)	0 (0.0)
Blood Bilirubin Increased	1 (0.0)	0 (0.0)	1 (0.2)
Hepatic Enzyme Increased	1 (0.0)	0 (0.0)	0 (0.0)
Liver Function Test Abnormal	0 (0.0)	4 (0.5)	0 (0.0)
Transaminases Increased	0 (0.0)	0 (0.0)	1 (0.2)

Tables 7.10.H and 7.10.I describe mean changes in liver function tests in both the ST and LT phases of the Phase 2 and 3 studies, respectively. The observed mean decreases in hepatic enzymes in the muraglitazar- and pioglitazone-treated groups may in fact be evidence of transaminase normalization; it is likely that treatment with muraglitazar has overall beneficial effects on the liver by reducing hepatic triglyceride.

Treatment Group	N	ALT	N	AST	N	T. Bili
Non-Titrated						
MUR 2.5 mg	442	-3.45 (27.22)	442	-1.24 +/- 18.92	442	-0.03 +/- 0.21
MUR 5 mg	1118	-7.96 +/- 12.14	1118	-2.27 +/- 8.45	1117	-0.05 +/- 0.18
Initial or Titrated						
Any MUR ≤ 5 mg	1880	-6.40 +/- 16.86	1880	-2.03 +/- 11.67	1879	-0.04 +/- 0.19
Any PIO ≤ 45 mg	631	-7.70 +/- 23.35	631	-1.14 +/- 28.31	631	-0.02 +/- 0.22
PLACEBO	364	-0.83 +/- 16.86	364	-0.62 +/- 17.66	363	0.00 +/- 0.19

Adapted from BMS summary_clinsafety, Page 659

	Any Mur ≤ 5 N = 284	Any Pio ≤ 45 N = 89
ALT (U/L)	-6.01 (13.08)	-5.39 (11.84)
AST (U/L)	-2.15 (9.92)	-1.87 (5.92)
Total Bilirubin (mg/dL)	-0.01 (0.18)	0.01 (0.23)

BMS summary_clinsafety, Page 120

120-Day Safety Update

In the monotherapy studies (CV168006 and -018) there were no additional cases of liver function test abnormalities from those that were reported in the original filing. In study CV168021 (combination with glyburide, one additional subject (54 year old female,

muraglitazar 2.5 mg) had ALT > 5x ULN on Day 253. The subject was not discontinued due to this event, and the elevations resolved by Day 341. The subject had the following laboratory results (ALT, AST, and T. Bili) for the duration of the study:

Table 7.10.J.

	Day -39	Day 1	Day 54	Day 113	Day 166	Day 201	Day 253	Day 257	Day 267	Day 341
ALT	34	17	18	19	17	15	171	150	46	20
AST	21	14	17	13	13	14	83	68	27	19
TBILI	0.5	0.4	0.3	0.3	0.4	0.3	0.4	NA	NA	0.4

NA = not available

In the metformin combination study CV168022 there were two subjects treated with muraglitazar who had ALT > 3x ULN (but < 5x ULN) and two who had AST > 3x ULN in the Safety Update. No subject had total bilirubin > 2 mg/dL in the Update. There were no discontinuations due to liver laboratory abnormalities in the Update.

7.11 Myopathy/Rhabdomyolysis/Creatine Kinase Elevation

Myopathy is a rare adverse effect of fibrate (PPAR- α) therapy, with much of the literature devoted to the interaction of statins in the pathogenesis of fibrate-related myotoxicity. Fibrate monotherapy leading to myopathy and rhabdomyolysis is likely a pharmacodynamic effect, related to altered fatty acid metabolism resulting in increased protein breakdown in the myocyte.⁷

Clinical Pharmacology

There was one subject in the clinical pharmacology studies with a discontinuation due to creatine kinase (CK) elevation. Subject CV168046-1-11, a 21 year-old white male, was discontinued due to an asymptomatic elevation in serum creatine kinase (CK) after receiving coadministration of a single dose of 10 mg muraglitazar with 160 mg fenofibrate. The subject had received muraglitazar 10 mg for seven days previously and undergone an off-site washout interval. The predose laboratory test results were received by the site after the administration of the dose, revealing a CK of 10,390 U/L. Please see Table 7.11.A for a complete listing of this subject's abnormal laboratory values. The investigator reported the subject had lifted heavy furniture during the washout interval.

⁷ Owczarek J, et al. Drug-Induced Myopathies. An Overview of the Possible Mechanisms. Pharmacological Reports 2005 57:23-34.

Table 7.11.A

Days	Visit	CK (U/L)	ALT (U/L)	AST (U/L)	LDH (U/L)
-1	P1 Day-1	150	26	27	203
8	P1 Day 8	105			
15	P2 Day -1	10390	84	124	707
15	P2 Day -1	21680		213	997
17	P2 Day 2	17300			
22	DISCHRG	528	58	42	186
22	DISCHRG	568	55	41	225
28	UNSCHED	140			

Phase 2 and 3

There was one event of rhabdomyolysis in the clinical program. Subject CV168021-110-2 (muraglitazar 5 mg + glyburide) was a 55 year-old Hispanic male, with a 10 year history of type 2 diabetes. Significant prior medical history included angiofibroma tumor of the nose, erectile dysfunction, myalgia and left knee injury. On study Day 175, the subject experienced an SAE of elevated creatinine kinase (CK) and rhabdomyolysis. Prior to this SAE, on day 169 (last day of the short-term phase) the subject's CK value was 4605 U/L (normal range: 34-221 U/L); however, the subject continued into the long-term phase. On Day 171, the CK value was 8513 U/L; the subject reported increased physical activity (yard work) on Days 166 and 167. The subject had not received a statin or fibrate at any time during the study but did take sildenafil 50 mg on Day 166. The subject reported anxiety, palpitations, dyspnea, neck stiffness and chest pain on Day 175 and was admitted for further evaluation. CK was reported to be approximately 900 U/L on admission. Cardiac tests (i.e. ECG and dobutamine echocardiography) were unremarkable and serum creatinine remained unchanged from baseline. The subject was treated with intravenous fluid hydration and a beta-blocker. The hospitalization lasted approximately 24 hours and the subject was discharged with a CK of approximately 500 U/L and residual dyspnea and anxiety. The last dose of study medication was taken on Day 175 and the subject discontinued from the long-term phase the same day. Urine myoglobin results obtained on Day 175 were positive with a value of 11 (normal range: 0-5). On Day 183, the investigator submitted SAEs of elevated CK levels and rhabdomyolysis with an onset on Day 175 and resolution on Day 176. The applicant considers the relationship of this event to muraglitazar to be uncertain because the CK level decreased (8000 to 900 U/L) prior to drug discontinuation. CK obtained eight days after discontinuation of study medication was 147 U/L.

The Preferred Term *myopathy* was noted in one subject. Subject CV168006-215-1 (muraglitazar 20 mg) had serial (4) AEs of *myopathy*, eventually leading to study discontinuation. The subject had a baseline CK of 220 U/L that increased to 310-484 U/L throughout the study with concomitant complaints of muscle ache.

There were 10 subjects who discontinued due to adverse events of elevated CK in the Phase 2 and 3 studies (ST and LT phases): one subject on muraglitazar 1.5 mg, one on muraglitazar 2.5 mg, four on muraglitazar 5 mg, one on a rescue dose of muraglitazar 10 mg from 5 mg, two on muraglitazar 20 mg, and one on pioglitazone 15 mg. Three of

these events were coded as SAEs (two subjects on muraglitazar 5 mg, one of whom was described above in the narrative; and one on muraglitazar 20 mg); none were on concomitant statin therapy.

The incidence of elevated CK (> 10x ULN) in the ST studies was comparable for subjects on all doses of muraglitazar (9 of 3174, 0.3%), placebo (2 of 583, 0.3%), and pioglitazone (2 of 812, 0.2%). The CK elevations were not associated with adverse events of *myalgia* or *muscle ache* except for one subject on pioglitazone (this subject was not receiving concomitant statin or fibrate therapy). Table 7.11.B demonstrates that treatment with muraglitazar in the ST phase was associated with a small dose-related increase in creatine kinase (CK) from baseline at Week 24.

Table 7.11.B. Mean Change from Baseline in CK at Week 24, Muraglitazar up to 5 mg						
Parameter	Non-titrated Dose			Initial or Titrated Dose		
	MUR 1.5	Any MUR 2.5	Any MUR 5	Any MUR ≤ 5	Any PLA	Any PIO ≤ 45
	N= 177	N= 535	N=1296	N=2374	N= 528	N= 823
Creatinine Kinase (CK) (U/L)						
N	139	442	1118	1880	362	632
Baseline Mean (SD)	123.3 (139.0)	130.1 (182.0)	110.0 (91.42)	117.7 (122.4)	114.5 (92.33)	106.2 (82.80)
Mean Change from Baseline (SE)	-4.71 (11.78)	-7.19 (7.79)	14.17 (4.67)	7.02 (3.53)	6.59 (8.76)	10.51 (2.76)

BMS summary_clinsafety, Page 113

In the LT studies, a higher mean increase was noted for subjects treated with muraglitazar ≤ 5 mg (29.03 U/L) than for pioglitazone-treated subjects (10.40 U/L) at Week 104. This appears to be due to individual elevations in a few select subjects. Four out of 459 (0.9%) of subjects on muraglitazar ≤ 5 mg and no pioglitazone-treated subjects in the LT phase of treatment had CK > 10x ULN. At the higher doses of muraglitazar (10 and 20 mg), six subjects experienced elevated CK > 10x ULN. No subject in either the ST or LT phase with CK elevation > 10x ULN had impairment in renal function as assessed by serum creatinine values reported in the database at the time of the laboratory abnormality.

Table 7.11.C presents the incidence of adverse events of CK elevation (Preferred Term *blood creatine phosphokinase increased*) in the Phase 2 and 3 studies, by individual study and pooled, as seen in the protocol column. The Phase 3 studies (CV168018, -021, and -022) and all studies combined indicate a possible dose-related increase in AEs of CK elevation (and a greater rate than pioglitazone or placebo), but this is not a consistent finding across studies.

Table 7.11.C. Number (%) of Subjects with AE of Preferred Term, Blood Creatine Phosphokinase Increased, ST Phase			
Protocol	Dose (mg)	N	Subjects (%) with AE
CV168006	Mur 0.5	236	7 (3.0)
	Mur 1.5	259	7 (2.7)
	Mur 5	245	6 (2.4)
	Mur 10	249	9 (3.6)
	Mur 20	239	8 (3.4)
	Pio 15	251	5 (2.0)
CV168008	Mur 5	64	1 (1.6)
	Mur 10	61	1 (1.6)
	Mur 20	66	1 (1.5)
	Mur 20 + Prava 40	66	4 (6.1)
	Placebo	63	2 (3.2)
CV168018, -021, and -022	Mur 2.5	535	7 (1.3)
	Mur 5	512	10 (1.9)
	Placebo	528	4 (0.8)
	Mur 5 OL	109	4 (3.7)
CV168025	Mur 5+Met	587	6 (1.0)
	Pio 30+Met	572	4 (0.7)
Total	Mur 2.5	535	7 (1.3)
	Mur 5	1408	23 (1.6)
	All Pio	823	9 (1.1)
	All Placebo	591	6 (1.0)

Additionally noted in this table is the numerical increase in the incidence of events of increased CK in the setting of add-on statin therapy in the mixed dyslipidemia study CV168008, increasing the rate from 1.5% in the muraglitazar 20 mg group to 6.1% in the muraglitazar 20 mg + pravastatin 40 mg group. However, none of these subjects had CK levels > 10x ULN.

Concomitant use of statin with the muraglitazar treatment (about 20% of subjects receiving muraglitazar) or fibrate (about 1% of subjects receiving muraglitazar) was not associated with a mean increase in CK, nor an increased risk of CK > 10x ULN in the clinical studies. As noted in Section 11, co-administration of muraglitazar with statins or fibrates had no clinically significant effect on the pharmacokinetics of either drug.

8 COMMON ADVERSE EVENTS

In the placebo-controlled clinical pharmacology studies, adverse events that occurred more frequently in healthy subjects receiving muraglitazar than placebo included peripheral edema, tachycardia, dizziness, and vomiting. In a 28-day inpatient study in subjects with type 2 diabetes adverse events that occurred more frequently with muraglitazar than placebo included peripheral edema, tachycardia, nausea, constipation, chest pain, and musculoskeletal pain.

In the Phase 2 and 3 studies, edema-related events were the most commonly reported adverse events in muraglitazar-treated subjects and are discussed in Section 7.3. In the ST type 2 diabetes studies pooled, total adverse events were reported for 68.6% of

subjects in the muraglitazar \leq 5 mg group, 68.4% of subjects in the placebo group, and 61.7% of subjects in the pioglitazone \leq 45 mg group, as seen in Table 8A (taken from the NDA, which excludes AEs of edema and hypoglycemia, as these were considered separately by the applicant).

Table 8A. Common AEs Reported by \geq 5% of Subjects (by SOC or PT) for Subjects with Type 2 Diabetes, Muraglitazar up to 5 mg Pooled, ST Phase			
System Organ Class (%) Preferred Term (%)	Any MUR \leq 5 N = 2374	Any PLA N = 528	Any PIO \leq 45 N = 823
Total Subjects With AE	1629 (68.6)	361 (68.4)	508 (61.7)
Infections And Infestations	798 (33.6)	184 (34.8)	246 (29.9)
Nasopharyngitis	164 (6.9)	43 (8.1)	42 (5.1)
Upper Respiratory Tract Infection	151 (6.4)	38 (7.2)	45 (5.5)
Musculoskeletal And Connective Tissue Disorders	487 (20.5)	100 (18.9)	139 (16.9)
Arthralgia	147 (6.2)	27 (5.1)	37 (4.5)
Gastrointestinal Disorders	413 (17.4)	93 (17.6)	144 (17.5)
Diarrhoea	108 (4.5)	28 (5.3)	41 (5.0)
Nervous System Disorders	365 (15.4)	80 (15.2)	105 (12.8)
Headache	160 (6.7)	40 (7.6)	43 (5.2)
Respiratory, Thoracic And Mediastinal Disorders	227 (9.6)	57 (10.8)	59 (7.2)
Investigations	217 (9.1)	26 (4.9)	53 (6.4)
Injury, Poisoning and Procedural Complication	211 (8.9)	46 (8.7)	58 (7.0)
General Disorders and Administration Site Conditions	172 (7.2)	30 (5.7)	45 (5.5)
Skin and Subcutaneous Tissue Disorders	168 (7.1)	33 (6.3)	41 (5.0)
Vascular Disorders	150 (6.3)	29 (5.5)	46 (5.6)
Psychiatric Disorders	94 (4.0)	28 (5.3)	32 (3.9)

BMS summary_clinsafety Page 50

Monotherapy, ST: Excluding edema and hypoglycemia, the most common adverse events in all three treatment groups were seen in the *Infections and Infestations* system organ class (SOC), with nasopharyngitis, arthralgia, headache, upper respiratory tract infection, diarrhea, pharyngolaryngeal pain, and bronchitis as the most common Preferred Terms (PT). Incidence was similar among treatment groups. Only arthralgia was seen more frequently on muraglitazar (6.2%) than placebo (3.5%).

Combination therapy, ST: The most common AEs observed in the combination therapy studies were similar to those seen in the monotherapy studies. Rates of AEs for muraglitazar 5 mg in combination with metformin in study CV168025 were comparable with rates of AEs for pioglitazone 30 mg with metformin.

During the long-term phase of the dose-ranging monotherapy study CV168006, the overall profile of AEs for up to two years was consistent with that seen at 24 weeks. The incidence of AEs between the muraglitazar and pioglitazone groups appeared similar with the exception of *weight increased*. A dose dependent increase in the incidence of the *weight increased* adverse event was seen for muraglitazar (ranging from 0% for the 1.5 mg non-titrated dose to 16.7% for the 5 mg non-titrated-dose). The incidence of the *weight increased* AE for pioglitazone was 8.9%.

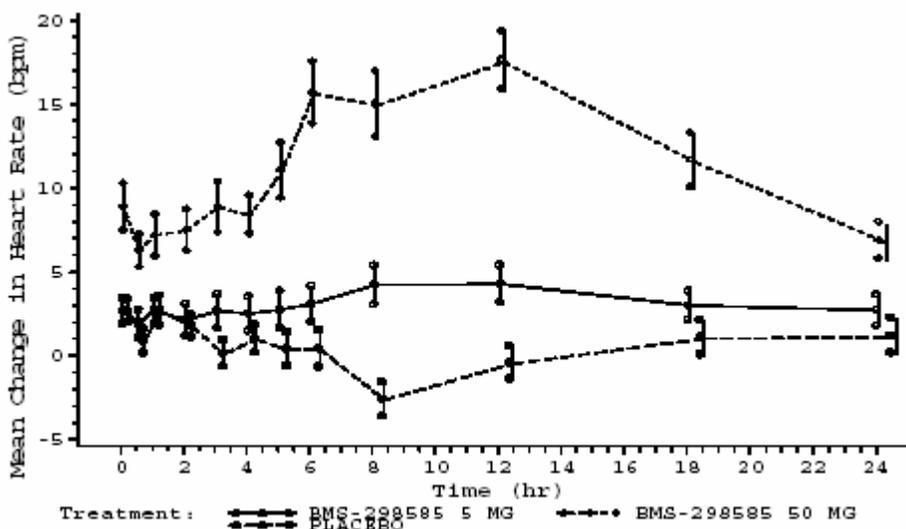
9 VITAL SIGNS

9.1 Heart Rate

In the clinical pharmacology studies, 28-day administration of high doses of muraglitazar (20 - 50 mg) was associated with small increases in heart rate (sinus rhythm) in both healthy and diabetic subjects. Doses < 20 mg appeared to be without effect on heart rate. Single doses of up to 300 mg were also without effect as compared to placebo.

In the thorough QT study (CV168043), the intensity of ECG sampling uncovered a small effect on heart rate not previously noted in vital signs, even with single doses up to 300 mg or multiple doses up to 50 mg for 28 days. A trend for a dose-related increase in heart rate was seen after eight days of dosing, and one subject was discontinued for sinus tachycardia. Figure 9.1.A illustrates the time-matched change in heart rate over time for placebo, 5 mg, and 50 mg muraglitazar on Day 8 in study CV168043.

Figure 9.1.A. Time-Matched Change from Baseline Heart Rate versus Time after Dosing on Day 8



BMS clinpharm_iss, Page 64

Table 9.1.A lists the adverse events of tachycardia in the clinical pharmacology studies. Tachycardia AEs appeared to occur more frequently in subjects who received higher doses of muraglitazar during multiple-dose administration. There was no apparent pattern for onset, duration, or severity of tachycardia.

Subject	MUR Dose	Start Time of AE	Duration of AE	Maximal Heart Rate
CV168002-1-10†	0.25 mg	4 days after Day 28 dose	Not reported	Not reported
CV168004-1-111‡	5 mg	19 minutes after Day 5 dose	4 days	Not reported
CV168004-1-66‡	20 mg	9.5 hours after Day 9 dose	12 hours	Not reported
CV168004-1-99‡	20 mg	18.5 hours after Day 4 dose	2.5 hours	Not reported
CV168043-1-1‡	50 mg	23 hours after receiving 8 daily doses	22 hours	133 bpm
CV168043-1-2‡	50 mg	5 hours after Day 8 dose	19 hours	142 bpm
CV168043-1-27‡	50 mg	2 days after receiving 8 daily doses	7.5 hours	105 bpm

BMS clinpharm_ISS Page 52

Note: † Type 2 Diabetic; ‡ Healthy Subject

In the Phase 2 and 3 studies, tachycardia AEs were seen infrequently throughout the clinical program: two subjects on muraglitazar 1.5 mg, four subjects on muraglitazar 5 mg, three subjects on muraglitazar 10 mg, one subject on muraglitazar 20 mg, two subjects on pioglitazone, and one subject on placebo. No subject was discontinued due to tachycardia.

9.2 Blood Pressure

In this submission, blood pressure was considered an efficacy variable, and will therefore be discussed in this Section only as far as individual cases, such as hypertensive crisis and malignant hypertension, are relevant to safety.

There were four serious adverse events of abnormal blood pressure in three subjects in the ST phase, and no events leading to study discontinuation. Narratives for the muraglitazar subjects follow.

Subject ID	Treatment Group	Preferred Term	Days
CV168021-303-29	MUR 2.5	Hypertensive Crisis	113
CV168025-48-6	MUR 5	Malignant Hypertension	64
CV168025-48-6	MUR 5	Hypertensive Crisis	114
CV168021-187-4	PLACEBO	Hypertensive Crisis	161

Subject CV168021-303-29 (muraglitazar 2.5 mg plus glyburide) experienced diabetic mononeuropathy and hypertensive crisis on Day 113 (very severe and moderate in intensity, respectively), which required hospitalization. The subject experienced a very severe headache localized to the frontal and left cranial areas and was treated with acetaminophen (3 gm on Day 113 through Day 116). Blood pressure on study Day 113 was 160/90 mmHg. The subject was treated with atenolol, ibuprofen, and captopril. The events both resolved on study Day 137. Blood pressure on study Day 154 was 112/60 mmHg. Study medication was not interrupted.

Subject CV168025-48-6 (muraglitazar 5 mg plus metformin) with a past medical history of hypertension and bilateral lower extremity edema, had one event of malignant hypertension and heart failure, and one event of hypertensive crisis:

- On Day 64, the subject presented to his primary care physician with a blood pressure of 190/120 mmHg, a sensation of pressure in the chest and difficulty breathing. The subject was subsequently admitted for worsening malignant hypertension. Heart failure was diagnosed by radiologic and echocardiographic findings. Additional diagnostic tests (i.e. MRA renal arteries, renal sonogram, aldosterone and renin levels, TSH, and urine electrolytes) for hypertension were unremarkable. The subject was discharged on Day 68 with improved BP control and the event was considered resolved that same day. Study medication was interrupted at the time of the event and resumed upon hospital discharge.
- On Day 114, the subject presented to his primary care physician with a BP of 168/110 mmHg and complaints of myalgias and arthralgias of approximately one month duration. The subject was hospitalized for a hypertensive crisis; BP was 183/112 mmHg on admission. Mild edema of the lower extremities was noted and the subject complained of polyuria, polydipsia, nocturia, weight gain (4.3 kg since Day 58) and anxiety. The hypertension was treated with nifedipine, furosemide, enalapril, and doxazosin with decreases into the 130/80 mmHg range. The patient was discharged on Day 116 and the event was considered resolved. Study medication was interrupted at the time of the event. The subject continued in the study.

10 ECG FINDINGS (QT_c)

Please see Dr. El Hage's Pharmacology/Toxicology briefing document for the results of preclinical QT findings.

Clinical Pharmacology

Study CV168043 was designed to evaluate the potential for muraglitazar to prolong QT_c in healthy subjects at the proposed therapeutic dose of 5 mg and a supra-pharmacological dose (50 mg) compared to placebo. The study was a randomized, double-blind, placebo-controlled, multiple-dose, crossover study, which was preceded by a double-blind, randomized crossover phase with moxifloxacin as positive control. The primary QT_c assessment was based on the maximum value of QT_c corrected by Fridericia's method (QT_{cF}) following exposure to the study drug.

QT_c intervals were also evaluated in a single ascending-dose study (CV168001), where healthy subjects were exposed to muraglitazar doses up to 300 mg. Multiple-dose studies were performed in healthy subjects and subjects with type 2 diabetes (CV168004 and CV168002, respectively), in which subjects received muraglitazar doses up to 50 mg daily for 28 days.

The applicant concluded that study CV168043 was a negative QT study at both doses tested (muraglitazar 5 mg and 50 mg), with QT_{cF} (Fridericia's correction) prolongation seen only with the positive control, moxifloxacin 800 mg. However, their calculation,

comparing the greatest placebo-subtracted maximum change in QTcF from baseline between groups, is not consistent with ICH E14 guidelines, which specify that QTcF differences from placebo must be time-matched, and then the greatest difference be used to establish the effect on QT interval. The Office of Clinical Pharmacology and Biopharmaceutics (OCPB)'s recalculation is shown in Table 10A, which indicates that muraglitazar 50 mg does in fact have a QT effect (upper 95% confidence interval > 10 msec). This suprathreshold dose is 10 times the highest proposed dose, muraglitazar 5 mg, which did not demonstrate an effect on QT interval. The applicant's calculation of moxifloxacin 800 mg QTc max was 16.5 msec more than placebo, and was not recalculated using this method by OCPB.

Table 10A. OCPB Recalculation of QTc Data, Study CV168043				
Time Point	Muraglitazar 5mg		Muraglitazar 50mg	
	Mean Difference	Upper 95% CI	Mean Difference	Upper 95% CI
0	0.148	4.264	5.631	8.953
1	0.556	4.749	3.806	7.975
2	-0.238	4.438	7.063	11.458
3	3.037	6.475	8.009	12.422
4	-1.620	2.664	5.856	10.885
5	2.056	5.662	2.238	6.312
6	1.048	4.897	7.306	11.993
8	0.009	4.022	4.919	9.972
12	0.185	4.257	2.351	7.282
18	-2.602	2.710	-1.432	3.333
24	-3.065	0.865	3.126	7.041

In study CV168043, one subject each on placebo, muraglitazar 5 mg, and muraglitazar 50 mg had $\Delta\text{QTcF} \geq 30$ to < 60 msec. No subject had a $\Delta\text{QTcF} \geq 60$ msec or $\text{QTcF} > 450$ msec.

In study CV168001, in which eight healthy subjects were assigned to each of six sequential muraglitazar dose panels (0.5, 1.5, 5, 25, 100, and 300 mg or matched placebo):

- No QTc interval exceeded 450 msec when corrected by either Bazett's or Fridericia's method.
- No QTcB change from baseline exceeded 57 msec. The largest number of subjects having a 30 to 60 msec change from baseline was in the placebo group (4/12), followed by the 300 mg (3/6) and 0.5 mg (2/6) groups.
- No QTcF change from baseline exceeded 34 msec, with one of six subjects treated with 0.5 mg and 5 mg having changes of 30-60 msec.

In study CV168002, in which 10 type 2 diabetic subjects were assigned (muraglitazar, n = 6; pioglitazone, n = 2; matched placebo, n = 2) to each of five separate sequential panels of muraglitazar (0.25 mg, 1.5 mg, 5 mg, 20 mg, or 50 mg daily for 28 days), the following ECG findings were noted when QT was corrected by Bazett's method:

- One of six subjects treated with muraglitazar 50 mg had a QTcB interval > 500 msec (508 msec) post dosing. The subject had a baseline QTcB interval of 497 msec.
- One of seven subjects treated with muraglitazar 0.25 mg had a QTcB interval change from baseline exceeding 60 msec (87 msec). The prolonged QTcB interval occurred at trough (24 hours post dosing) on Day 15.
- Eight of 32 (25%) subjects treated with muraglitazar and two of 10 (20%) placebo-treated subjects had QTcB interval increases from baseline between 30-60 msec.

When corrected by Fridericia's method, subjects on study CV168002 had the following findings:

- No subject had a QTcF interval exceeding 500 msec.
- One subject treated with muraglitazar 50 mg had a QTcF interval between 480-500 msec. This subject had a baseline QTcF of 470 msec and a screening QTcF of 482 msec, and no change from baseline that exceeded 14 msec.
- Six of 32 (19%) subjects treated with muraglitazar (all doses) had at least one QTcF interval between 450-480 msec. No subjects treated with pioglitazone or placebo had a QTcF interval between 450-480 msec.
- One of seven subjects treated with muraglitazar 0.25 mg had a QTcF increase from baseline exceeding 60 msec (67 msec at trough on Day 15). No QTcF interval for this subject exceeded 452 msec.
- Five of 32 (16%) subjects treated with muraglitazar and one of 10 (10%) subjects treated with placebo had QTcF interval increases from baseline between 30-60 msec.

In study CV168004, where 120 healthy subjects were randomly assigned to receive muraglitazar 5 mg (n = 30), muraglitazar 20 mg (n = 60), or matching placebo (n = 30), for 28 days, no clinically significant changes from baseline in average or maximum QTc intervals were observed with either muraglitazar 5 mg or 20 mg groups at study Day 28, although the 20 mg dose demonstrated statistical significance (Table 10B).

Table 10B. Study CV168004: Change from Baseline in QTc Intervals (msec) and 95% Confidence Limits for Study Day 28					
		Mean Change from Baseline	95 % CI	P-value vs. Placebo	P-value vs. MUR 5 mg
Change from Baseline in Average of QTc Intervals	MUR 20 mg	3.62	1.44, 5.79	0.08	< 0.001
	MUR 5 mg	-3.09	-6.16, -0.01	0.12	-
	Placebo	0.33	-2.69, 3.35	-	0.12
Change from Baseline in Maximum of QTc Intervals	MUR 20 mg	5.24	1.33, 9.15	0.99	0.09
	MUR 5 mg	-0.68	-6.21, 4.84	0.14	-
	Placebo	5.20	-0.22, 10.62	-	0.14

Adapted from BMS cv168004, Page 292

In the 678 subjects treated with muraglitazar in the 20 US clinical pharmacology studies combined (Table 10C), no subject had a post-dose QTcF interval greater than 500 msec. Table 10D demonstrates that 49 subjects (~8%) treated with muraglitazar had a QTcF increase from baseline between 30-60 msec while 13 placebo-exposed subjects (13%) and 18 subjects (~18%) exposed to active control treatments had similar changes. Three subjects (0.5%) exposed to muraglitazar and one placebo subject (1%) had a prolongation in QTcF \geq 60 msec as compared to baseline (Δ QTcF).

10C. Number (Percent) of Subjects with Borderline or Prolonged QTcF (msec) for All Treated Subjects						
		Mur Only N = 518	Mur Plus N = 124	Any Mur N = 628	Active Other N = 116	Placebo N = 98
Male	N	358	117	461	93	58
	\leq 450	352 (98.3)	116 (99.1)	454 (98.5)	92 (98.9)	58 (100.0)
	450 < QTcF \leq 480	6 (1.7)	1 (0.9)	7 (1.5)	1 (1.1)	0 (0.0)
	> 480	0	0	0	0	0
Female	N	160	7	167	23	40
	\leq 450	153 (95.6)	7 (100.0)	160 (95.8)	23 (100.0)	39 (97.5)
	450 < QTcF \leq 480	5 (3.1)	0 (0.0)	5 (3.0)	0 (0.0)	1 (2.5)
	480 < QTcF \leq 500	2 (1.3)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)
	> 500	0	0	0	0	0
Total	N	518	124	628	116	98
	\leq 450	505 (97.5)	123 (99.2)	614 (97.8)	115 (99.1)	97 (99.0)
	450 < QTcF \leq 480	11 (2.1)	1 (0.8)	12 (1.9)	1 (0.9)	1 (1.0)
	480 < QTcF \leq 500	2 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
	> 500	0	0	0	0	0

Adapted from clinpharm_iss, Page 277

10D. Number (Percent) of Subjects with Borderline or Prolonged Change from Baseline QTcF (msec) for All Treated Subjects						
		Mur Only N = 517	Mur Plus N = 124	Any Mur N = 627	Active Other N = 102	Placebo N = 98
Male	N	357	117	460	79	58
	< 30	324 (90.8)	113 (96.6)	424 (92.2)	73 (92.4)	51 (87.9)
	30-60	31 (8.7)	3 (2.6)	33 (7.2)	6 (7.6)	6 (10.3)
	> 60	2 (0.6)	1 (0.9)	3 (0.7)	0	1 (1.7)
Female	N	160	7	167	23	40
	< 30	144 (90.0)	7 (100.0)	151 (90.4)	11 (47.8)	33 (82.5)
	30-60	16 (10.0)	0	16 (9.6)	12 (52.2)	7 (17.5)
	> 60	0	0	0	0	0
Total	N	517	124	627	102	98
	< 30	468 (90.5)	120 (96.8)	575 (91.7)	84 (82.4)	84 (85.7)
	30-60	47 (9.1)	3 (2.4)	49 (7.8)	18 (17.6)	13 (13.3)
	> 60	2 (0.4)	1 (0.8)	3 (0.5)	0	1 (1.0)

Adapted from clinpharm_iss, Page 279

Phase 2 and 3

In a sub-study of Phase 2 study CV168006, 497 randomized subjects with type 2 diabetes had ECGs collected at baseline and at Week 12. In Phase 3 study CV168018, ECGs were

collected at baseline and at Week 24. The Week 24 ECGs were performed both pre-dose and 3 hours post-dose. Both studies evaluated for QTc prolongation.

Table 10E describes the findings of the QT testing at baseline and Week 12 in study CV168006. Muraglitazar-treated groups were slightly higher than the pioglitazone-treated group with respect to the mean Δ QTcB and Δ QTcF at Week 12. Five subjects had a change from baseline in QTcB (Bazett's correction) to Week 12 > 60 msec, but none of the maximum QTcB intervals exceeded 480 msec. No subject in any of the treatment groups had a Δ QTcF > 60 msec at Week 12. The proportion (mean) of muraglitazar-treated subjects with $30 \geq \Delta$ QTcF < 60 msec was slightly higher than the pioglitazone-treated subjects (8% versus 5%).

10E. Study CV168006: Number (%) Subjects with QTc Greater than 500 msec and Change from Baseline to Week 12, ST Phase						
	MUR 0.5 mg	MUR 1.5 mg	MUR 5 mg	MUR 10 mg	MUR 20 mg	PIO 15 mg
Baseline						
≤ 500 msec	100 (100)	93 (100)	104 (100)	84 (100)	103 (100)	99 (100)
> 500 msec	0	0	0	0	0	0
Week 12						
≤ 500 msec	62 (100)	71 (100)	83 (100)	77 (100)	91 (100)	66 (100)
> 500 msec	0	0	0	0	0	0
Change from baseline (msec), Bazett						
N	61	69	82	71	91	65
Mean (SD)	5.67 (18.88)	1.25 (21.49)	1.84 (21.38)	1.48 (23.35)	4.12 (24.22)	0.37 (18.18)
Median	6.00	1.00	1.50	4.00	8.00	5.00
Range	-51, 47	-47, 42	-52, 62	-78, 63	-61, 75	-42, 36
Change from baseline (category), Bazett						
≤ 60 msec	61 (100%)	69 (100%)	81 (99%)	70 (99%)	89 (99%)	65 (100%)
> 60 msec	0	0	1 (1%)	1 (1%)	2 (2%)	0
Change from baseline (msec), Fridericia						
N	61	69	82	71	91	65
Mean (SD)	5.57 (18.04)	2.03 (19.07)	2.80 (18.51)	2.97 (18.33)	2.04 (21.75)	1.69 (17.35)
Median	6.00	4.00	5.00	6.00	3.00	3.00
Range	-45, 37	-44, 45	-50, 56	-61, 37	-59, 56	-45, 37
Change from baseline (category), Fridericia						
≤ 60 msec	61 (100%)	69 (100%)	82 (100%)	71 (100%)	91 (100%)	65 (100%)
> 60 msec	0	0	0	0	0	0

Adapted from BMS cv168006st, Page 2901

In Phase 3 study CV168018, the mean changes from baseline to Week 24 (pre- and post-dose) in the QTcF or QTcB interval were smaller in the muraglitazar treatment groups (2.5 mg and 5 mg) compared to the placebo group (Tables 10F-10I). No subject had a Δ QTcF ≥ 60 msec (Tables 10F and 10H). One subject on placebo and one subject on muraglitazar 5 mg OL had Δ QTcB ≥ 60 msec (81 and 74 msec, respectively; Table 10G). The muraglitazar 5 mg OL subject also had a Δ QTcB of 75 msec post-dose (Table 10I). One percent (1%) of the subjects treated with muraglitazar 5 mg and 2% of subjects treated with placebo had a post-dose QTcF interval exceeding 450 msec at Week 24 (Table 10L); the rates were slightly higher using the Bazett's calculation in all treatment groups (Table 10M). No subject had a QTcF > 480 msec (Tables 10J and 10L). One

subject in the muraglitazar group and one subject in the placebo group had a pre-dose QTcB between 480 and 500 msec (Table 10K).

Table 10F. Study CV168018: Changes from Baseline to Week 24 Pre-Dose for QTc (Fridericia) Interval in msec During the Double-Blind Phase and in the Open-Label Cohort					
Treatment	N	Mean	SD	Median	Range
MUR 2.5	78	3.8	14.25	4.5	-37, 40
MUR 5	78	3.0	17.75	6.0	-35, 53
PLA	83	6.1	16.47	4.0	-29, 54
MUR 5 OL	64	1.3	16.29	1.5	-36, 52

Adapted from BMS cv168018, Page 1708

Table 10G. Study CV168018: Changes from Baseline to Week 24 Pre-Dose for QTc (Bazett) Interval in msec During the Double-Blind Phase and in the Open-Label Cohort					
Treatment	N	Mean	SD	Median	Range
MUR 2.5	78	3.1	18.02	2.5	-40, 57
MUR 5	78	1.9	21.53	4.0	-47, 45
PLA	83	7.8	21.32	8.0	-39, 81
MUR 5 OL	64	0.8	21.37	1.5	-41, 74

Adapted from BMS cv168018, Page 1710

Table 10H. Study CV168018: Changes from Baseline to Week 24 Post-Dose for QTc (Fridericia) Interval in msec During the Double-Blind Phase and in the Open-Label Cohort					
Treatment	N	Mean	SD	Median	Range
MUR 2.5	88	-0.4	16.46	-1.0	-41, 32
MUR 5	92	-0.1	18.50	0.0	-46, 49
PLA	94	0.6	17.16	2.0	-41, 41
MUR 5 OL	73	0.2	18.85	1.0	-42, 55

Adapted from BMS cv168018, Page 1712

Table 10I. Study CV168018: Changes from Baseline to Week 24 Post-Dose for QTc (Bazett) Interval in msec During the Double-Blind Phase and in the Open-Label Cohort					
Treatment	N	Mean	SD	Median	Range
MUR 2.5	88	-2.5	21.46	-2.0	-49, 52
MUR 5	92	-3.0	22.31	-3.5	-60, 39
PLA	94	1.5	21.23	0.0	-57, 49
MUR 5 OL	73	-1.2	24.02	1.0	-58, 75

Adapted from BMS cv168018, Page 1714

Table 10J. Study CV168018: Shift table of Baseline versus Week 24 Pre-Dose QTc (Fridericia) Interval during the Double-Blind Phase and in the Open-Label Cohort				
	QTc Interval (msec) Baseline	Week 24 Pre-Dose		
		≤ 450	> 450 – 480	> 480
MUR 2.5 mg	≤ 450	78	0	0
	>450 - 480	0	0	0
	>480	0	0	0
MUR 5 mg	≤ 450	75	1	0
	>450 - 480	0	2	0
	>480	0	0	0
PLA	≤ 450	82	1	0
	>450 - 480	0	0	0
	>480	0	0	0
MUR 5 mg OL	≤ 450	63	0	0
	>450 - 480	1	0	0
	>480	0	0	0

Adapted from BMS cv168018, Page 1688

Table 10K. Study CV168018: Shift table of Baseline versus Week 24 Pre-Dose QTc (Bazett) Interval during the Double-Blind Phase and in the Open-Label Cohort					
	QTc Interval (msec) Baseline	Week 24 Pre-Dose			
		≤ 450	> 450 – 480	> 480 – 500	>500
MUR 2.5 mg	≤ 450	72	3	0	0
	>450 - 480	2	1	0	0
	>480	0	0	0	0
MUR 5 mg	≤ 450	70	1	1	0
	>450 - 480	3	3	0	0
	>480	0	0	0	0
PLA	≤ 450	79	2	1	0
	>450 - 480	1	0	0	0
	>480	0	0	0	0
MUR 5 mg OL	≤ 450	57	2	0	0
	>450 - 480	3	2	0	0
	>480	0	0	0	0

Adapted from BMS cv168018, Page 1690

Table 10L. Study CV168018: Shift table of Baseline versus Week 24 Post-Dose QTc (Fridericia)				
Interval during the Double-Blind Phase and in the Open-Label Cohort				
	QTc Interval (msec) Baseline	Week 24 Post-Dose		
		≤ 450	> 450 – 480	> 480
MUR 2.5 mg	≤ 450	88	0	0
	>450 - 480	0	0	0
	>480	0	0	0
MUR 5 mg	≤ 450	90	0	0
	>450 - 480	1	1	0
	>480	0	0	0
PLA	≤ 450	92	2	0
	>450 - 480	0	0	0
	>480	0	0	0
MUR 5 mg OL	≤ 450	72	0	0
	>450 - 480	1	0	0
	>480	0	0	0

Adapted from BMS cv168018, Page 1692

Table 10M. Study CV168018: Shift table of Baseline versus Week 24 Post-Dose QTc (Bazett)					
Interval during the Double-Blind Phase and in the Open-Label Cohort					
	QTc Interval (msec) Baseline	Week 24 Post-Dose			
		≤ 450	> 450 – 480	> 480 – 500	>500
MUR 2.5 mg	≤ 450	84	1	0	0
	>450 - 480	3	0	0	0
	>480	0	0	0	0
MUR 5 mg	≤ 450	82	4	0	0
	>450 - 480	5	1	0	0
	>480	0	0	0	0
PLA	≤ 450	89	4	0	0
	>450 - 480	1	0	0	0
	>480	0	0	0	0
MUR 5 mg OL	≤ 450	63	3	0	0
	>450 - 480	6	1	0	0
	>480	0	0	0	0

Adapted from BMS cv168018, Page 1694

11 CLINICAL PHARMACOLOGY

Muraglitazar is rapidly absorbed after oral administration, with peak plasma concentrations occurring in 0.5 to 6 hours (median: 3 hours). Plasma concentrations increase in a dose-proportional manner up to 20 mg. With once daily administration, steady-state concentrations are achieved within seven days, with a terminal half-life of approximately 24 hours (range: 19 to 31 hours). The accumulation index at steady-state ranges from 1.5 to 1.9. Muraglitazar is highly bound to human plasma (99.9%), and is mainly excreted in the feces with biliary elimination as the major clearance pathway; renal elimination is negligible (< 4%).

In Phase 1 studies, muraglitazar plasma pharmacokinetics did not appear to differ in subjects with type 2 diabetes when compared with healthy subjects, nor did the pharmacokinetic profile vary by gender. There was no effect of age on the C_{max};

however, there was an increase in AUC (26%) in elderly (65 to 79 years) versus younger (20 to 40 years) subjects. In addition, population pharmacokinetic analyses in subjects aged 20 to 70 years with type 2 diabetes demonstrated that pharmacokinetics were not influenced by age, body weight, race, or gender. Muraglitazar pharmacokinetics in subjects with mild hepatic impairment (Child-Pugh Class A) was similar to healthy matched control subjects. In subjects with moderate or severe impaired hepatic function (Child-Pugh Class B/C), there was a 2- to 3-fold increase in AUC values when compared with matched control subjects.

Muraglitazar is a substrate for multiple CYP P450 enzymes including CYP 3A4, 2C19, 2C9, 2C8, and 2D6 in humans. In vitro, muraglitazar was a moderate inhibitor of CYP 2C9 and 2C8. No clinically meaningful drug-drug interactions were observed in pharmacokinetic studies. Co-administration of muraglitazar with HMG CoA reductase inhibitors (atorvastatin, simvastatin, or pravastatin), fibrates (gemfibrozil or fenofibrate), or antihyperglycemic agents (glyburide or metformin), did not affect the pharmacokinetics of either drug. The administration of warfarin or famotidine did not affect the pharmacokinetics of muraglitazar. There was a 43% increase in muraglitazar AUC with co-administration of ketoconazole.

12 APPENDIX

The following are narratives for the deaths in the clinical program.

Initial Filing

Subject CV168006-5-3 (MUR 10 mg) was a 62 year-old white female who was in a motor vehicle accident after 112 days of treatment. The subject was waiting at a stop light when her car was struck by a semi-truck. She was pronounced dead on arrival at the hospital.

Subject CV168006-10-1 (PIO 15 mg) was a 66 year old white male was diagnosed with cancer of the throat after 679 days of treatment. Three months prior, on Day 591, he reported moderate pain and difficulty swallowing. The subject underwent subsequent laryngoscopy, bronchoscopy and esophagoscopy. A biopsy confirmed advanced squamous cell cancer of the piriform sinus (throat cancer). Chemotherapy and radiation therapy were initiated. Five weeks after the diagnosis, the subject died suddenly at the hospital. Relevant medical history includes a two-month history of type 2 diabetes mellitus, hypertension, hypercholesterolemia, a 45-year history of cigarette smoking, prior alcohol abuse (quit 2000), cirrhosis, jaundice, esophageal varices, BPH, decreased hearing, hemorrhoids, GERD, diverticulitis, gallstones, and appendectomy. Concomitant medications included: omeprazole, nadolol, multivitamin, loperamide, ketorolac, dicyclomine, promethazine, trimethoprim/sulfamethoxazole, APAP/hydrocodone, dexamethasone, and 5- FU. Other adverse events reported post-randomization included: right flank pain (Day 79), diarrhea (Day 83), right knee pain (Day 130), weight gain (Day 207), back pain (Day 252), hypoglycemic symptoms (Day 252), cough (Day 255) and gastritis (Day 289).

Subject CV168006-11-8 (MUR 20 mg) was a 59 year old white male diagnosed with type 2 diabetes for two years prior to the study. Significant medical history included previous tobacco use (stopped 7 years prior to study entry), hypertension, iron overload with fatty liver, and psoriasis. On study Day 43 the subject experienced the non-serious adverse event of bilateral pitting edema in his ankles, considered mild in intensity and probably related to study medication; no treatment was required and it did not resolve. He developed dyspnea and was admitted to the hospital from the emergency room on Day 49 with an initial diagnosis of congestive heart failure secondary to a myocardial infarction. The subject reported that he had some increased exertional dyspnea while mowing his lawn for the previous month. He denied any prior chest pain (including upon presentation). Follow-up information from the investigator indicated that his diagnosis at admission was myocardial infarction (MI). Cardiac enzyme levels (see table below) were markedly elevated and supportive of the MI diagnosis. The investigator considered this serious adverse as not likely to be related to study medication and the subject was discontinued. The subject deteriorated throughout Day 49; he was intubated and coronary artery bypass surgery scheduled for Day 50 was cancelled. On Day 50, a cardiac catheterization was performed. The procedure revealed a 99% left main arterial distal stenosis; left anterior descending artery of moderate size with minimal luminal irregularity but no clinical stenosis; circumflex artery of moderate size with minimal luminal irregularities but no significant stenosis; and the right coronary artery was a small vessel with a “critical proximal long stenosis noted from approximately 80%”. An echocardiogram was immediately performed to evaluate left ventricle function and rule out critical aortic stenosis. The results of the echocardiogram included a moderately dilated left ventricle with severe global hypokinesis; normal size left atrium; mild mitral insufficiency; and “ejection fraction to about 15 - 20% at best”. An intra-aortic balloon pump was placed because of chest discomfort, which dissipated once the balloon was paced on one-to-one augmentation. On Day 60 life support was withdrawn in accordance with his previously expressed wishes and the patient died. The causes of death as listed on the death certificate were “1) Myocardial infarction - 5 days, 2) Coronary Artery Disease- 5 years, and 3) Diabetes – 5 years.”

Cardiac enzyme measurements

Day	Time	CPK (U/L)	CK-MB (ng/mL)	Troponin (ng/mL)
		Normal range 30-265 U/L	Normal Range < 4.0 ng/mL	Normal Range < 0.5 ng/mL
Day 49	11:55	518	65.2	2.46
Day 49	16:00	968	NA	5.65
Day 49	23:30	1461	NA	12.17
Day 50	5:00	2251	296.2	23.99
Day 50	10:05	2931	233.9	45.75

NA = not available

Subject CV168006-255-1 (MUR 1.5 mg) was a 69 year-old white Hispanic male, diagnosed four years prior to the study with type 2 diabetes. Significant medical history included anaplastic stomach carcinoma treated surgically four years prior to the screening visit, peripheral vascular disease, obesity, previous cigarette (quit 1989) and alcohol use. On Day 476, he was hospitalized for “wasting syndrome,” including symptoms of asthenia and tiredness and a 10 kg weight loss in the month prior to hospitalization. Study medication was stopped on Day 473 and he was discontinued from the study on Day 497. He underwent endoscopy, abdominal ultrasound and CT scans to determine the cause of the wasting syndrome; the investigator initially suspected that it was a recurrence of the subject’s stomach cancer. The results of the CT scans revealed multiple pulmonary endobronchial masses, liver abnormalities, and splenomegaly. Laboratory values for total bilirubin and alkaline phosphatase were elevated. A biopsy done during subsequent bronchoscopy was negative for cancer but the interpretation of the imaging and clinical situation indicated that this represented a second new tumor with pulmonary location and the subject was diagnosed with pulmonary carcinoma. An oncology consult determined that he was not eligible for any chemotherapy because of his deteriorated physical condition. He was discharged from the hospital on Day 498, and re-hospitalized on Day 503. The subject died on Day 505.

Subject CV168006-267-5 (MUR 1.5 mg) was a 69 year old white female diagnosed six months prior to the study with type 2 diabetes. Relevant medical history included hypertension, mixed dyslipidemia, moderate alcohol use, hysterectomy, osteoarthritis, renal colic and solar keratosis. On Day 537 the subject was diagnosed with severe acute myeloid leukemia. Two months prior to the diagnosis, on Day 477, the subject’s blood sample revealed abnormal red blood cell morphology. Bone marrow aspiration was performed on Day 538 (results unavailable). The subject was treated with blood and platelet transfusions and intravenous antibiotics. Six weeks after the diagnosis the subject died. At the time of the event, the subject was receiving the following concomitant medications: atenolol, lacidipine, simvastatin, acetylsalicylic acid, losartan, indapamide, amoxicillin/clavulanate, and allopurinol.

Subject CV168008-02-12 (MUR 20 mg + pravastatin 40 mg) was a 65-year old white male, diagnosed in 1992 with mixed dyslipidemia. Upon entering the long-term phase of the study, the subject was reallocated to receive MUR 20 mg alone. Significant medical history included: hypertension, obesity, hypercholesterolemia, hypertriglyceridemia, mixed dyslipidemia, alcoholism, and prior cigarette smoking (quit in 1975). On study Day 439, the subject was involved in a motor vehicle accident and died. No postmortem findings were available. The investigator considered the event as not related to study medication. At the time of the event, the subject was receiving the following concomitant medications: terazosin, acetylsalicylic acid, and multivitamins. Post randomization the subject also had adverse events of intermittent dizziness (on days 2 and 17).

Subject CV168021-298-21 (MUR 5 mg + glyburide) was a 44 year-old (at enrollment) white male, diagnosed three years prior to the study with type 2 diabetes. Significant prior medical history included history of being overweight, hypercholesterolemia, and

impotence. On study Day 29, the subject died as a result of a gun shot wound. The site was not notified of the subject's death until study Day 102 despite attempts to contact subject by phone and registered mail.

Subject CV168022-153-2 (MUR 5 mg + metformin) was a 54 year-old (at enrollment) white man, diagnosed six years prior to the study with type 2 diabetes. Investigational study drug was administered for a total of 115 days. Significant prior medical history included obesity, hypertension, coronary artery disease, coronary thrombosis and a cardiac catheterization six years prior to the study. On study Day 115, the subject presented to the emergency room with complaints of abdominal bloating, increasing dyspnea, orthopnea and lower extremity edema. He reported increased swelling of his legs and ankles over the past 2 to 3 months, with the swelling worsening over the past 3 to 4 days. On physical exam, he had bibasilar rales and 1+ pitting edema of the lower extremities. Views of the chest, included as part of an abdominal survey (x-ray), taken for abdominal distention, revealed no acute findings. An ECG showed Q waves in leads III, V1, V2, V3 and V4 suggestive of an inferior infarction and extensive anterior infarction (age indeterminate), left axis deviation, and left atrial enlargement. The ECG was not significantly changed from baseline. There was no elevation in cardiac enzymes (CKMB and troponin-I). While hospitalized, the subject was treated with a single dose of furosemide 40 mg I.V., aspirin, metoprolol, and glimepiride. The subject was discontinued from the study on Day 115 as a result of this SAE. The SAE was reported to have resolved on Day 116. The subject was discharged from the hospital after 23 hours for further outpatient cardiac evaluation. On Day 116, the subject returned to work. On Day 117, a chest x-ray was done by the investigator that was reported as normal. On Day 118, the subject returned to the investigator's site and had a body weight of 300 lbs., an increase of 10 lbs. from the previous study visit on Day 90. NT-proBNP was elevated at screening (548 pg/mL), prior to the event (Day 68 = 1085 pg/mL, Day 90 = 1027 pg/mL) and on Day 118 (1236 pg/mL). The subject refused to have a physical exam done and failed to comply with the recommended outpatient cardiac evaluation. On study Day 125, the subject was found dead in his home. The death certificate listed myocardial infarction and occult coronary artery disease as the cause of death. At the time of the SAE, the subject was receiving the following relevant medications: metformin 2000 mg/day, amlodipine, benazepril, and niacin.

Subject CV168022-256-6 (MUR 5 mg + metformin) was a 56 year-old (at enrollment) Hispanic female diagnosed 10 years prior to the study with type 2 diabetes. Investigational study drug was administered for a total of 45 days. Significant prior medical history included cancer of right breast 12 years prior to study entry, hypertension, obesity, hypercholesterolemia, hypertriglyceridemia, mixed dyslipidemia, diabetic retinopathy, cholecystectomy, current tobacco use, and hysterectomy (without hormone replacement). On study Day 27, the subject was diagnosed with multiple osseous metastases of recurrent breast cancer (very severe intensity) following a bone scan. The bone scan was prompted by recurrent back pain, which first presented two days prior to randomization, and was unrelieved by diclofenac sodium and physiotherapy. The breast cancer was thought to have been in remission. No treatment was given for the metastases. The subject was discontinued as a result of this SAE on Day 45. From Day 94 to 106 and from Day 119 to 126, she was hospitalized for

gastrointestinal hemorrhage. This event was attributed to chronic gastritis and esophageal candidiasis after endoscopy during the first visit. Her hematocrit during her first hospitalization was 14% (baseline range: 33% to 43%). The subject subsequently died from cardiopulmonary arrest as a complication of cancer on Day 149, 105 days after her last dose of investigational study drug.

Subject CV168022-287-1 (MUR 2.5 mg + metformin) was a 52 year-old (at enrollment) Hispanic man, diagnosed four years prior to the study with type 2 diabetes. Investigational study drug was administered for a total of 10 days. Significant prior medical history included: hypertension, obesity, hypercholesterolemia, hypertriglyceridemia, mixed dyslipidemia, and alcohol use (two drinks on most days). On study Day 10, the subject had a sudden onset of chest pain and died suddenly. Postmortem evaluation confirmed the occurrence of a myocardial infarction (very severe intensity). The subject had no history of ischemic heart disease. At the time of the event, the subject was receiving the following relevant concomitant medications: metformin 2000 mg/day, atorvastatin, and lisinopril.

Subject CV168025-241-003 (MUR 5 mg + metformin) was a 67-year-old white male who was diagnosed with type 2 diabetes 14 years prior to study entry. Significant prior medical history included: ischemic heart disease, hypertension, congestive heart failure, stable angina, history of obesity, varicose disease, hypercholesterolemia, hypertriglyceridemia, bilateral lower extremity fluid retention, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, chronic bronchitis, chronic otitis, neurosensory bradyacusia, lower extremity onychomycosis, deforming arthrosis and tobacco use. On Day 144, the subject experienced a serious adverse event of sudden death. The subject died suddenly after someone broke into his home. The death certificate listed the cause of death as chronic ischemic heart disease. An autopsy was not performed. This subject was taking enalapril at the time of this event. The investigator considered the event not related to study medication.

Subject CV168025-242-29 (PIO 30 mg + metformin) was a 67-year-old white male who was diagnosed with type 2 diabetes 13 years prior to study entry. Significant prior medical history included lumbar osteochondrosis, obesity, hypertension, diabetic neuropathy, diabetic retinopathy, diabetic angiopathy of the lower extremities, fatty hepatosis, nephroptosis, urolithiasis and kidney cysts (for >1 year), chronic prostatitis, dyscirculatory encephalopathy and current tobacco use. On Day 36, the subject experienced a serious adverse event of urolithiasis (severe in intensity). The subject was hospitalized with urolithiasis in the lower third of the right ureter and pyelonephritis. Ureterolithotomy of the right lower third kidney was performed and a drainage stent placed on Day 36. On Day 39 the subject had an acute perforated duodenal bulb ulcer (serious adverse event of very severe intensity) and died that same day. The following concomitant medication was being taken at the time of the event: enalapril. An additional adverse event of epigastric pain (Day 28) was reported after randomization.

Subject CV168025-314-1 (MUR 5 + metformin) was a 53-year-old white male diagnosed with type 2 diabetes six years prior to study entry. Significant prior medical history

included hypertension, stable and unstable angina, coronary artery disease, coronary artery bypass graft, history of obesity, hypercholesterolemia and tobacco use. On Day 107, the subject experienced a serious adverse event of stroke (severe in intensity). The subject experienced symptoms of headache and vertigo on Day 107 and was hospitalized with right-sided paralysis due to a severe stroke. The subject died on Day 110. The subject had previously reported numbness in both arms on Day 36. The following concomitant medications were being taken at the time of this event: amlodipine, atorvastatin, candesartan, metoprolol, acetylsalicylic acid, and diclofenac. The investigator considered the event not related to study medication.

120 Day Safety Update

Subject CV168006-80-9 (MUR 5 mg) was a 70 year-old white female, diagnosed with type 2 diabetes for approximately two years prior to the study. Significant medical history included COPD, current cigarette smoking (1½ ppd x 47 years), recurrent bronchitis, hypertension, obesity, DVT of left leg, gallbladder removal, premature menopause, hysterectomy, hypothyroidism, hypercholesterolemia, osteoporosis, arthritis, eczematous skin disorder-granuloma annulare, alcohol use, generalized fatigue, anxiety, claustrophobia, and codeine allergy. Baseline physical exam was notable for abnormal lung exam with bronchial cough. Baseline CXR revealed no infiltrates or effusions, slight tortuosity of the aorta, mild kyphosis and no change from the previous CXR. The subject complained of episodic fatigue and COPD exacerbations since 2002. AEs of worsening fatigue (Day 685), bronchitis (Day 751), shortness of breath (Day 730) and worsening cough prompted a helical CT scan of the chest on Day 752 which showed a 1.5 cm diameter right upper lobe nodule surrounded by additional lung parenchymal density; most likely tumor; metastatic nodules scattered throughout liver; right hilar and right superior mediastinal adenopathy. This was documented as a SAE of metastatic lung cancer. The subject was treated with theophylline and prednisone. She also underwent MRI of lumbar spine for lower extremity pain, weakness and gait instability which showed mild lumbar scoliosis and compression deformity of L1. A mammogram was done which was negative. The event resulted in death on Day 808.

Subject CV168021-33-5 (PLA + glyburide) was a 62 year-old (at enrollment) white male who was diagnosed four years prior to the study with type 2 diabetes. Treatment was administered for a total of 244 days. Significant prior medical history included hypertension, hyperlipidemia, hypertriglyceridemia, obesity, asbestos exposure in the right lung, cholelithiasis and prior tobacco use. On Day 244, the subject experienced sudden death due to massive pulmonary emboli. The subject complained of shortness of breath on the evening prior to the event which continued into the morning. The patient was found dead and emergency medical services were subsequently called. An autopsy revealed that both the right and left pulmonary arteries were completely occluded by emboli with phlebothromboses of the left popliteal vein and veins of the left calf musculature. At the time of the event, the subject was receiving treatment with atorvastatin, lisinopril and hydrochlorothiazide. Post randomization the subject had no other adverse events.

Subject CV168021-237-5 (MUR 5 mg + glyburide) was a 56 year-old (at enrollment), Hispanic/Latino female, diagnosed five years prior to the study with type 2 diabetes. Significant prior medical history included hypertension, unstable angina (hospitalization), obesity, mixed dyslipidemia, varicose syndrome, appendectomy, cesarean operation, cerebrovascular accident without sequelae, diabetic retinopathy, anxiety, and depression. On Day 307, the subject experienced an acute myocardial infarction. The subject presented to a local Emergency Department but was subsequently transferred to another medical institution. Initial findings included tachypnea, dyspnea, stupor, hyperglycemia, and metabolic acidosis. ECG showed sinus rhythm with ST segment depression in the anterior leads. The subject received nitroglycerin, heparin, acetylsalicylic acid, clopidogrel, and insulin. On Day 311, a chest x-ray showed bilateral infiltrates and a SAE of acute heart failure was reported (very severe intensity). The subject required intubation and mechanical ventilation on study Day 312. On Day 313, non-sustained ventricular tachycardia (VT) developed during the placement of a Swan-Ganz catheter. The VT subsided and atrial fibrillation (SAE, severe intensity) developed but was successfully treated with cardioversion. By Day 317, the subject had received the following additional treatments: fentanyl, enalapril, furosemide, potassium, sucralfate, atenolol, sucralfate, spironolactone, dobutamine ampicillin, sulbactam, and hydrocortisone. On Day 318, a second SAE of atrial fibrillation (severe intensity) was reported with spontaneous resolution. The subject experienced arrhythmias of extreme bradycardia and ventricular fibrillation (Day 320, both events were reported as SAEs of very severe intensity) that required advanced cardiovascular life support measures. Resuscitation efforts were not successful and the subject expired on Day 321.

Subject CV168022-142-4 (MUR 5 mg + metformin) was a 63 year-old (at enrollment) white female diagnosed 10 years prior to the study with type 2 diabetes. Significant prior medical history included hypercholesterolemia, hypertriglyceridemia, nodular goiter, appendicitis, osteoporosis, sulfa and penicillin allergy, benign hyperkeratotic acanthoma and prior tobacco use for 35 years. On Day 206, the subject was diagnosed with small cell cancer of the lung with metastasis to brain, adrenal and liver (very severe intensity). The subject presented to the ER complaining of “altered mental status”. Diagnostic tests including a chest x-ray, MRI, CT scan and bronchoscopy confirmed the diagnosis. The subject was treated with dexamethasone 16 mg, amaryl 4 mg, protonix 40 mg, and regular insulin. The patient was discharged from the hospital on Day 210. The patient was discontinued from the study but did not return for the final visit. The subject subsequently died on Day 326 due to this event.

Subject CV168022-250-15 (MUR 2.5 mg + metformin) was a 51 year-old white Hispanic male with a diagnosis of type 2 diabetes for three years prior to the study. Investigational study medication was administered for a total of 195 days. Significant prior medical history included retinopathy, ametropia, calcaneal spur right foot, prior alcohol use (heavy drinker until 8 years prior to the study), and tobacco use. On Day 189, the subject presented to his primary care physician (PCP) with complaints of very mild and diffuse abdominal pain and mild distension. On Day 193, symptoms worsened and the PCP prescribed tegaserod for non-specific colitis. On Day 195, the abdominal pain intensified and the subject was hospitalized. An abdominal ultrasound showed hypoechoic lesions

on the liver and a CT scan showed an enlarged liver with multiple nodular lesions, an enlarged pancreas and ascites. The subject was discharged. On Day 208, the subject returned to the hospital and required removal of two liters of ascites. A liver biopsy obtained on Day 210 showed the presence of well differentiated hepatocellular carcinoma. The subject was discharged with pain medication and died at home on Day 224 due to complications from the hepatocellular carcinoma.

Subject CV168025-193-9 (MUR 5 mg + metformin) was a 66 year-old white female diagnosed with type 2 diabetes four years prior to study entry. Significant prior medical history included hypertension, peripheral vascular disease, transient ischemic attack, bilateral lower extremity fluid retention, atrial flutter/mitral insufficiency, obesity, chronic bronchitis, microalbuminuria, history of being overweight and tobacco use. Physical examination at screening revealed bilateral pitting edema of both feet and ankles. On Day 202 the subject experienced a serious adverse event of sudden death due to myocardial infarction. The investigator reported an event of dyspnea due to heart decompensation on the evening before the subject died. An autopsy was not performed and cause of death was reported as myocardial infarction.

Subject CV168025-193-10 (MUR 5 mg + metformin) was a 61 year-old white male diagnosed with type 2 diabetes three years prior to study entry. Significant prior medical history included myocardial infarction, peripheral vascular disease, peripheral vascular surgery, coronary artery disease, mixed dyslipidemia, bilateral lower extremity fluid retention, hypothyroidism, history of being overweight/obesity, and alcohol and tobacco use. On Day 169, the subject completed the 24-week short-term phase of the study and entered the long-term period. On Day 211 the subject was found dead. A forensic physician reported the subject died due to natural causes on Day 208, the cause of death was not specified, and no further investigations were performed. At the time of this event the subject was receiving pravastatin.

Safety Update; June 9, 2005

The applicant presented findings of additional deaths after unblinding of study CV168025:

Subject CV168025-241-38 (MUR 5 mg + metformin) was a 60-year-old white female with a 24 year history of type 2 diabetes prior to study entry. Significant prior medical history included hypertension; obesity; diabetic nephropathy, neuropathy, and retinopathy; and environmental exposure to tobacco. On Day 282, the subject was hospitalized and died on Day 293 from a cerebrovascular accident. The patient's son reported that his mother was hospitalized for worsening hypertension and suffered a stroke. Based on this, the investigator initially reported the hospital admission to be for hypertension. The autopsy report indicated the reason for admission was "ischemic heart disease" and that the subject had a stroke on Day 290. The autopsy described the fatal event as follows: "In patient with hypertension and atherosclerosis (cerebral) massive hemorrhage in left cerebral hemisphere developed with brain hematoma forming, with hemorrhage rupture into ventricular system, ventricular tamponade. Increasing brain edema and brain displacement were the reason of death." Additional autopsy findings

included: myocardial hypertrophy, mild atherosclerosis of the aorta, heart arteries and brain; obesity; lipomatosis of the pancreas, and bilateral pneumonia. The only concomitant medication reported prior to the hospitalization was enalapril.

Subject CV168025-288-65 (MUR 5 mg + metformin) was a 50 year-old mulatto female with an 11-year history of type 2 diabetes prior to study entry. Significant prior medical history included obesity, hypertension, menopause, and right shoulder pain. At the time of screening, there were no known risk factors for liver disease, markers for viral hepatitis were negative, total bilirubin was normal, and ALT and AST were slightly elevated as was the alkaline phosphatase (350 IU/L). During the two-week lead-in period, the subject had two AEs of diarrhea, an AE of diarrhea on Day 57, and an AE of flu on Day 87. The subject had AEs of moderate back pain on Days 41 and 77. The subject lost 2.5 kg from screening to randomization and a total of 8.5 kg from screening to Day 114. On Day 114 the subject experienced serious adverse events of cholestasis and head of pancreas carcinoma with liver metastasis, and symptoms of nausea, abdominal pain, jaundice and choluria. The symptoms persisted until Day 134 when she presented to the Emergency Department. The subject was hospitalized with a total bilirubin of 8.6 mg/dL, ALT 209 IU/L and AST 226 IU/L. On Day 138, an abdominal ultrasound found no abnormalities in the intrahepatic bile ducts or evidence of bile duct stone. A CT scan on Day 139 showed a hypodense lesion on the left hepatic lobe. Liver function tests remained elevated and alkaline phosphatase was 1702 IU/L. A CT scan with contrast on Day 140 confirmed the hepatic lesion and normal intra-and extrahepatic biliary tract. A 10 cm liver mass was subsequently biopsied on Day 176 and diagnosed as a metastatic lesion from an undifferentiated pancreatic (head) carcinoma. The subject received palliative treatment and was discharged with elevated ALT, AST, total bilirubin and alkaline phosphatase. Study medication was discontinued as a result of these events. The subject died 108 days after discontinuing study medication.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Julie Golden
8/5/05 11:52:30 AM
MEDICAL OFFICER

David Orloff
8/5/05 12:07:13 PM
MEDICAL OFFICER