ADVISORY COMMITTEE BRIEFING DOCUMENT

PARGLUVA™

(MURAGLITAZAR, BMS-298585)

NDA 21-865

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

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1 INTRODUCTION

Bristol-Myers Squibb Company filed a New Drug Application (NDA) for the use of Pargluva™ (muraglitazar) in the treatment of subjects with type 2 diabetes mellitus in December 2004. Since that submission additional data from the long-term portion of the ongoing studies have been obtained. These inclusive muraglitazar development program data are assessed in this briefing document as follows:

1) the "NDA Dataset" (data submitted to the FDA in December 2004)
2) the "Complete Dataset" (data from the NDA Dataset plus the 120 Day Safety Update submitted to the FDA in April 2005 and additional data for clinically important events from the long-term phase of studies CV168006, CV168021, CV168022, and CV168025). *(Note: This dataset includes safety information that may not be incorporated in the Agency's analysis).*

The "NDA Dataset" serves as the basis for assessing all clinical data, efficacy findings, and most safety findings that involve comparisons to either placebo or pioglitazone within specific study time frames. The "Complete Dataset" has been included in order to provide long-term information for muraglitazar treatment experience regarding deaths, heart failure and other cardiovascular (CV) events, cancers, and laboratory signals from liver function tests or creatine kinase (CK) monitoring.

Pargluva™, muraglitazar and BMS-298585 designate the same compound and may be used interchangeably. Also, in this document, "type 2 diabetes mellitus" and "type 2 diabetes" designate the same disease and may be used interchangeably.

This document is organized according to the following outline:

- Executive summary and overview of type 2 diabetes mellitus, PPARs and muraglitazar (Section 2)
- Development program for muraglitazar in the treatment of type 2 diabetes mellitus (Section 3)
- Non-clinical toxicology program (Section 4)
- Human pharmacokinetics program (Phase 1; Section 5)
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- On-going and planned non-clinical and clinical studies (Section 9)
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2 EXECUTIVE SUMMARY

2.1 Background Information on Type 2 Diabetes

Worldwide prevalence of diabetes mellitus was estimated to be 4% (135 million adults) in 1995.[1] Recently, an alarming increase in the prevalence of type 2 diabetes has been recognized across the globe. This increase is due in part to the adoption of Western diets and lifestyles and increases in the prevalence of obesity.[2] In the United States, the Centers for Disease Control and Prevention (CDC) estimated in 2002 that approximately 18 million adults (8.7% of all people 20 years and older) have diabetes, including 8.6 million adults who are 60 years or older (18.3% of this group).[3] Clinic-based reports and regional studies in the US indicate that type 2 diabetes is becoming more common among children and adolescents, particularly in American Indians, African Americans, and Hispanic/Latinos.[3] Overall, approximately 1.3 million new cases of diabetes are diagnosed each year in US residents aged 20 years or older.[3]

Concurrent with the emergence of this diabetes epidemic, several landmark clinical outcome studies have demonstrated that tight control of hyperglycemia lowers the risk of chronic microvascular diabetic complications such as retinopathy and nephropathy. The Diabetes Control and Complications Trial (DCCT)[4] in patients with type 1 diabetes and the United Kingdom Prospective Diabetes Study (UKPDS)[5] in patients with type 2 diabetes compared intensive to conservative glucose management and demonstrated a reduced risk of complications with better glucose control. These observations have established hemoglobin A1C (now termed A1C by the American Diabetes Association [ADA]) as the universal "report card" used by diabetes patients and physicians to track glucose control in order to attain near-normalization of glycemia as a fundamental component of optimal diabetes management. The impact of tight glycemic control on cardiovascular morbidity has recently been dramatically underscored by results of the ongoing DCCT/EDIC (Epidemiology of Diabetes Interventions and Complications) cohort long-term follow-up study.[6] These findings, reported at the ADA conference in June 2005, demonstrated a 57% reduction in the number of serious cardiovascular events such as myocardial infarctions and strokes among type 1 diabetes patients whose glycemic control was tightly managed to an A1C target of < 7% for 6.5 years during the

original DCCT study 10 years earlier.[7] This benefit is truly striking, as it was achieved even though less rigid glycemic control comparable to the standard care control group was maintained during the 10 year post-study period. The goal of achieving tight and durable glycemic control measured by A1C targets below 7% is buttressed strongly by these results.

Although type 2 diabetes mellitus has long been characterized as a primary disorder of glucose control, insights into its complex pathophysiology over the past several decades have modified this "glucocentric" view and emphasized the critical importance of other metabolic abnormalities. Insulin resistance, abnormal fatty acid and lipid metabolism, and possibly alterations in other circulating metabolic or hormonal factors can interfere with achieving desired glycemic control. Elevations in circulating fatty acids contribute to a loss of insulin sensitivity at important target organs like muscle and liver[8] and directly impair pancreatic islet beta cell function.[9] These metabolic derangements also play a direct role in the genesis of the high triglyceride/low HDL-cholesterol dyslipidemia (so-called "diabetic dyslipidemia") characteristic of type 2 diabetes.[10,11] Taken together, these factors create a CV risk for patients with type 2 diabetes that is equivalent to that of a non-diabetic patient with a prior myocardial infarction and contribute to the high rates of CV morbidity and mortality suffered by most diabetes patients.[12] Concomitant lipid abnormalities are believed to be an important factor because approximately two thirds of adults with type 2 diabetes have dyslipidemia. Consequently, treatment of lipid abnormalities such as elevated triglyceride (TG) and/or reduced high density lipoprotein cholesterol (HDL-C) levels has gained in importance.[13,14]

Available prospective cohort studies suggest that lipid abnormalities are associated with increased risk of CV events in patients with diabetes and have demonstrated that triglycerides (TGs) and HDL-C along with low density lipoprotein cholesterol (LDL-C), especially small dense LDL particles, are independent predictors of cardiovascular disease (CVD).[11,15] Although the favorable morbidity and mortality impact of achieving TG and HDL-C control is not as well established in clinical outcomes studies as LDL-C or glycemic control, the evidence is beginning to emerge. For example, the Veterans Affairs high-density lipoprotein intervention trial (VA-HIT) demonstrated a 19% reduction in CV events due to treatment with gemfibrozil; this effect was attributed to a

6% increase in HDL-C levels over a 3-4 year period. An even greater CV event reduction was reported recently in the subset of diabetic subjects evaluated in this trial.[16,17]

Thus, the interaction of multiple metabolic perturbations underlies the progressive pathophysiology and eventual morbidity of type 2 diabetes. For example, it has become clear that insulin resistance precedes and predicts the development of type 2 diabetes mellitus. Although exercise and weight loss help to ameliorate insulin resistance and have been shown to prevent or delay the onset of type 2 diabetes, these efforts are not always effective or sustainable. Therefore, therapy that directly treats insulin resistance as well as hyperglycemia is needed. The understanding of this fundamental aspect of type 2 diabetes provided the impetus for new treatments to decrease insulin resistance such as the current thiazolidinedione (TZD) peroxisome proliferator-activated receptor (PPAR) gamma agonists.[18] These insights have also led to more aggressive and comprehensive management approaches to the cardiovascular health of patients with type 2 diabetes.[19,20] Control of hyperglycemia and CV risk factors such as dyslipidemia is critical for optimum management of diabetes patients. The promise of simultaneous PPARγ and PPARα agonism to treat this constellation of metabolic components that characterize type 2 diabetes underpins the rationale for the development of dual PPAR activators such as muraglitazar.

2.2 Discovery and Background Information for PPARs

The PPARs are a subfamily of the 48-member nuclear-receptor superfamily and regulate gene expression in response to ligand binding. PPARs are likely involved with the pathogenesis of insulin resistance, diabetes and its related complications.[21] Three subtypes of PPAR have been identified (alpha [α], gamma [γ], and delta [δ]). PPARγ is expressed most abundantly in adipose tissue but is also found in pancreatic beta cells, vascular endothelium, and macrophages. PPARα is predominantly expressed in the liver, the heart, and skeletal muscle.

2.2.1 In Vivo and In Vitro Efficacy Findings of PPAR Agonists

PPARα and γ play a role in lipid metabolism, adipocyte maturation, and fatty acid storage. Activation of PPARγ improves insulin sensitivity and glucose utilization while

activation of PPARα leads to reductions in TG and elevations of HDL-C. In addition, experiments of both PPARγ and PPARα agonists in many animal studies have shown that activation of these two pathways can improve or prevent atherosclerosis through improvements in lipid abnormalities, inhibition of macrophage activation and foam cell formation, and through other cellular or metabolic pathways impacting the vascular wall.[18,22]

The discovery of PPARγ as the target for TZDs was followed by the discovery of several compounds that activate PPARγ, as well as activators of both PPARα and γ. In January 1997, the first TZD, troglitazone, was approved as a glucose-lowering therapy for patients in the United States with type 2 diabetes, but it was subsequently withdrawn from the market in March 2000 due to hepatotoxicity. Two currently available PPARγ agonists from the TZD class, rosiglitazone and pioglitazone, were approved in the United States in 1999 and have not shown this idiosyncratic hepatotoxicity.

Multiple metabolic effects have been described with the use of the TZD PPARγ agonists in clinical studies. Most notably, these agents increase insulin sensitivity in skeletal muscle, liver, and adipose tissue, and reduce levels of free fatty acids as a metabolic indicator of this improved insulin sensitivity.[18] Additional beneficial effects on adipocyte metabolic activity, endothelial function, procoagulant state, dyslipidemia, and blood pressure have also been described. Blood pressure reduction may occur via vasodilation due to the increased insulin sensitivity of resistance vessels, and/or direct effects on calcium uptake by vascular smooth muscle.[23,24,25] Reduction in blood pressure may increase renal sodium and water retention, or such renal responses may be directly activated by these compounds, possibly through direct activation of PPARγ receptors in the renal collecting duct.[26,27,28,29]

The TZDs rosiglitazone and pioglitazone are generally well tolerated and typically do not cause hypoglycemia when used as monotherapy because they do not stimulate insulin secretion. Side effects of concern with PPARγ agonists include weight gain, and adverse events of edema and, infrequently, events of heart failure.

2.2.2 Preclinical Carcinogenicity Findings for PPAR Agonists

Several PPARγ, PPARα, PPARδ, dual PPARα/γ and PPAR pan-agonists have been brought into development by a number of companies. The available data from rodent carcinogenicity studies (two-year studies in mice and rats) that have been completed for several PPAR agonists have recently been reviewed by the FDA. The results of these composite carcinogenicity studies demonstrate that PPAR agonists are tumorigenic in one or more rodent species and can act at multiple sites, sometimes in both sexes. The tumor types commonly observed include hemangiosarcomas in mice, transitional cell carcinomas of the urinary tract in rats, lipoma/liposarcomas in both species and sarcomatous tumors at multiple sites, such as kidney, stomach, uterus and skin. Because the tumors are located at sites known to have high concentrations of PPAR receptors and mechanistic data is not available to explain mode of action for many tumor types, a receptor-mediated mechanism and human relevance cannot be ruled out.

Currently, rodent carcinogenicity study results must be submitted for Agency review prior to the conduct of clinical studies lasting longer than six months. Clearly, each molecule with PPAR activity across the three PPARγ, PPARα, and PPARδ isoforms needs to be thoroughly evaluated and judged on its own specific preclinical characteristics. For this reason, muraglitazar has been evaluated with a rigorous investigational toxicology program to help determine the potential clinical significance of any pre-clinical carcinogenicity findings.

2.2.3 Clinical Safety Considerations of PPAR agonists

In addition to the efficacy findings described above in Section 2.2.1 for PPAR agonists, there are several clinical safety and tolerability manifestations associated with the use of marketed TZD PPARγ agonists. Mean dose-related weight gain of 2-4 kg is typically apparent after 6 months of therapy.[18,30,31,32] Some of this weight gain, as noted with other diabetes treatments such as insulin or sulfonylureas, is due to caloric retention in adipose tissue as glycosuria improves. PPARγ agonists also promote fat redistribution from visceral adipose tissue to subcutaneous adipose depots, leading to less adverse metabolic impact on the liver.[8] In addition, PPARγ agonists may cause dose-dependent fluid retention, which can lead to weight gain and peripheral edema in 4-8% of

patients.[18,30,31,32] Mild decreases in hematologic parameters, most likely due to hemodilution as a consequence of fluid retention, have been noted with pioglitazone and rosiglitazone. Finally, clinical events involving the precipitation or exacerbation of heart failure are infrequently observed with PPARγ agonists.

Currently available PPARα agonists belong to the class of fibrates. In the US, two PPARα agonists are available: gemfibrozil and fenofibrate. The fibrates as a class are well tolerated and the incidence of significant adverse effects is low. Adverse effects that have been reported include nausea, vomiting, abdominal discomfort, elevated liver enzymes, skin rashes, and allergic reactions. In addition, infrequent elevations in serum creatinine and unfavorable interactions with statins to raise creatine kinase have been observed with fibrates. Concern has also been raised regarding gallstone formation and myositis with fibrates, although the risk of these events using monotherapy treatment with currently available fibrates appears to be low.

2.3 Muraglitazar

Muraglitazar is the first of a new class of anti-diabetic drugs termed "glitazars." It is an oxybenzylglycine, non-thiazolidinedione PPAR dual agonist, active at both α and γ PPAR receptors. Muraglitazar has been extensively studied in both non-clinical and clinical studies.

2.3.1 Non-clinical Program of Muraglitazar

Non-clinical Pharmacology and Toxicology Studies:

Non-clinical studies demonstrate that muraglitazar exhibits potent binding to recombinant human PPARα and PPARγ receptors in vitro. Muraglitazar also induces efficient PPARα- and PPARγ-dependent transactivation of reporter gene expression in cell-based functional assays. Thus, muraglitazar possesses binding and activation properties characteristic of both PPARα and PPARγ, the intended molecular targets. Specificity is also apparent as muraglitazar does not bind to, or transactivate, a number of related nuclear hormone receptors, including the PPARδ isoform, the PPAR heterodimeric binding partner retinoid X receptor, estrogen receptor, or progesterone receptor.

In vivo, muraglitazar exhibits potent antihyperglycemic and lipid lowering activity in several animal models of diabetes, hyperglycemia, obesity, and hyperlipidemia. In a rodent model of diabetes (*db/db* mouse), muraglitazar improves insulin sensitivity and lipid metabolism. This effect is demonstrated by the correction of plasma glucose, insulin, triglycerides and free fatty acids to levels normally observed in the non-diabetic mouse model. Muraglitazar also maintains glycemic control, preserves pancreatic islet beta cell function, and increases pancreatic islet insulin content in a pre-diabetic rodent model (young *db/db* mouse).

The overall non-clinical safety program included studies evaluating the single-dose and repeat-dose toxicity, reproductive toxicity, adverse and pharmacologic activity in animals. Study durations extended up to 1 year in rats and monkeys. Muraglitazar was not hepatotoxic, myotoxic, or nephrotoxic in rats or monkeys at exposures 376 and 59 times, respectively, that achieved in humans at 5 mg. Muraglitazar was not teratogenic in rats or rabbits. It demonstrated no cardiac effects in monkeys at up to 17 times human exposure and only minimal reductions in blood pressure in dogs at 120 times maximum free drug concentrations at 5 mg.

Mutagenesis and Carcinogenesis Assessments:

The non-clinical safety program also included studies evaluating genotoxicity and carcinogenic potential in animals. Muraglitazar was not mutagenic or clastogenic in a battery of genetic toxicity studies including an in vitro Ames bacterial assay, an in vitro cytogenetics assay in peripheral human lymphocytes, and an in vivo oral micronucleus assay in rats. Two-year carcinogenicity studies were conducted in rats at oral doses of 1, 5, 30, and 50 mg/kg/day [highest dose equivalent to approximately 48 (males) and 59 (females) times the human AUC at the recommended human dose of 5 mg/day]. Two-year carcinogenicity studies were also conducted in mice at oral doses of 1, 5, 20, and 40 mg/kg/day [highest dose equivalent to approximately 141 (males) and 154 (females) times the human AUC at the recommended human dose]. In male rats, the incidence of benign and/or malignant transitional cell neoplasms of the urinary bladder was increased at muraglitazar doses $\geq$ 5 mg/kg/day (approximately 8 to 48 times human AUC at the recommended human dose). This finding is similar to findings in rats treated with pioglitazone and is considered not relevant to humans because urinary bladder neoplasms are considered to have occurred by a species-specific mechanism.

An increased incidence of subcutaneous liposarcomas in male rats and lipomas in female rats were observed at 50 mg/kg/day (approximately 48 to 59 times the human AUC at the recommended human dose). An increased incidence of adipocyte tumors has also been demonstrated in rats treated with rosiglitazone. The adipocyte findings with muraglitazar are considered not relevant to humans given that these tumors occurred at markedly higher systemic exposures then that at the recommended human dose.

In male mice, a low incidence of benign gallbladder adenomas was observed at doses of 20 and 40 mg/kg/day (approximately 62 and 141 times human AUC, respectively, at the recommended human dose). The increased incidence of benign gallbladder adenomas in male mice is considered of no established relevance to humans given that gallbladder adenomas occurred at markedly higher systemic exposures then that at the recommended human dose.

In summary, although some positive rodent carcinogenic findings were observed, the weight of evidence suggests that muraglitazar should not pose a carcinogenicity risk to humans at clinical doses and exposures. More detailed descriptions of non-clinical safety of muraglitazar are provided in Section 4. In addition, an extensive post-marketing pharmacovigilance program has been designed to address potential concerns and is described more fully in a separate pharmacovigilance plan submission and in Section 11.

2.3.2 Clinical Efficacy of Muraglitazar

The muraglitazar clinical program included **5448** subjects treated with muraglitazar or a comparator:

- **808** subjects in Phase 1 clinical pharmacology studies
  720 of these subjects were treated with muraglitazar
- **1797** subjects in Phase 2 clinical studies (includes 320 non-diabetics)
  1483 of these subjects were treated with muraglitazar
- **2843** subjects in Phase 3 clinical studies (in subjects with type 2 diabetes)
  1743 of these subjects were treated with muraglitazar.

Muraglitazar was studied in randomized controlled clinical studies in both monotherapy and combination therapy. The pharmacology of muraglitazar provides for simultaneous

PPARγ and PPARα activation to treat a broad range of metabolic defects in patients with type 2 diabetes. This rationale underpinned the choice, timing and design of clinical surrogate endpoint assessments that were incorporated into clinical studies to evaluate both glycemic and lipid efficacy of muraglitazar. All primary endpoints for glycemic efficacy were assessed at Week 24 while the primary assessments for lipid efficacy were evaluated at Week 12, before alterations (i.e., addition or change in dose) in concurrent lipid-lowering therapy with statins or other lipid-modifying agents were permitted per the protocol designs.

The composite results of five pivotal clinical trials submitted as part of the muraglitazar NDA have consistently demonstrated that muraglitazar has significant efficacy for improving both glycemic and lipid control in type 2 diabetes mellitus. Treatment with muraglitazar resulted in improvement in overall glycemia, as measured by reductions in A1C, fasting plasma glucose (FPG) and postprandial glucose levels. In addition, fatty acid elevations, fasting and postprandial hyperinsulinemia, and overall insulin sensitivity estimated through HOMA (homestasis modeling assessment) methods improved during muraglitazar treatment. Among components of diabetic dyslipidemia, there were improvements in TG, HDL-C, and apolipoprotein B (apoB) levels while overall LDL-C values did not change. The fall in apoB levels with stable LDL-C concentrations indicates that LDL particle numbers decreased. These LDL particles, therefore, are likely to possess less atherogenic characteristics with muraglitazar treatment by converting from a small, dense quality to larger and more buoyant particles. Finally, muraglitazar treatment resulted in decreases in several vascular and atherothrombotic biomarkers such as high sensitivity C-reactive protein (hs-CRP), plasminogen activator inhibitor-1 (PAI-1) and fibrinogen.

Glycemic and lipid lowering efficacy for type 2 diabetes patients was demonstrated as monotherapy and in combination with either metformin or a sulfonylurea. Importantly, in all monotherapy and combination studies, more subjects on muraglitazar than placebo or pioglitazone achieved A1C glycemic goals as defined by the ADA or the American Association of Clinical Endocrinologists (AACE). Muraglitazar treatment also led to sustained benefit, as the improvement in glycemic and lipid control with muraglitazar was durable in a cohort of subjects maintained at a 5 mg daily dose for up to 2 years.

Based on comparison of efficacy from the parallel dose arms in the Phase 2 dose-ranging study, upward titration of muraglitazar to a dose up to 10 mg may provide additional glycemic efficacy and add dyslipidemic efficacy as the need for supplemental efficacy arises through physician and/or patient monitoring of glycemic and lipid control. Thus, although not submitted as part of this NDA filing, additional clinical titration studies of muraglitazar up to 10 mg as monotherapy and in combination with metformin that complement the dose-ranging (Study CV168006) monotherapy trial are currently underway. These clinical trials are evaluating titration of muraglitazar in comparison to titration with pioglitazone or titration of a sulfonylurea in combination with metformin, and are currently envisioned to be submitted as future supplementary filings to FDA. Ultimately, starting with requested approval of the 2.5 mg and 5 mg doses submitted in this NDA, muraglitazar dose options should provide patients and physicians with a useful set of doses as well as guidelines for their use based on risk and benefit for achieving and maintaining glycemic and dyslipidemia control for comprehensive management of type 2 diabetes.

In addition to the randomized controlled trials described above, other future muraglitazar studies that are underway or planned include the use of muraglitazar when co-administered with insulin, its use in NYHA Class II heart failure patients with type 2 diabetes, and in elderly and pediatric patients. Finally, a long-term clinical outcomes study to characterize the CV benefits of muraglitazar (just beyond its effect on established surrogate markers) is planned. The specific design of this study will depend on the results of ongoing clinical outcomes studies with pioglitazone (PROactive) and fenofibrate, as well as results from other muraglitazar studies (FIELD),[33,34] as well as results from other muraglitazar studies. The long-term clinical outcomes information will continue to define the benefit and risk relationships of muraglitazar for appropriate populations in a rigorous manner that is complementary to other components of the future development program.

More details of the clinical efficacy of muraglitazar are provided in Sections 6 and 7.

2.3.3 Clinical Safety of Muraglitazar

The clinical safety of muraglitazar has been comprehensively evaluated in the NDA, providing clinical information in over 3200 subjects (2969 diabetic subjects) treated with

muraglitazar in Phase 2/3 studies, including 697 subjects treated for over 2 years. Importantly, more than 151 subjects have been treated with a daily dose of 10 mg muraglitazar for at least 24 months and more than 179 subjects have been treated with a daily dose of 20 mg muraglitazar for at least 18 months. This lengthy clinical experience on doses that are 2 to 4 times greater than the highest daily dose for which FDA approval is sought at the present time provides reassurance that adverse events related to prolonged high exposures or enhanced pharmacology have been thoroughly investigated. Indeed, evaluating these higher doses in Phase 2 allowed us to determine that glycemic efficacy and the occurrence of adverse events appear to be dose-dependent as the PPARγ activity of muraglitazar increases.

Summary of Results

Given current knowledge and experience with PPARγ TZDs, the muraglitazar NDA clinical program was designed to closely track weight gain, edema and heart failure adverse events. Reporting of edema was specifically requested for all subjects at each study visit in the large Phase 2 dose-ranging study and the use of an independent heart failure adjudication committee was included for Phase 3 studies. In addition, events of hypoglycemia as well as hematologic, liver and muscle CK laboratory testing abnormalities were also monitored closely given possible PPARγ and PPARα effects.

Analysis of other adverse events (excluding edema-related and hypoglycemia events) from all 24-week controlled clinical trials of muraglitazar 2.5 mg and 5 mg doses demonstrated that the incidence of adverse events reported in at least 5% of the subjects, regardless of causality, was similar between muraglitazar and placebo. In combination therapy, the incidence for most clinical adverse events was similar for groups treated with muraglitazar 2.5 mg and 5 mg in combination with metformin or sulfonylurea compared to the incidence reported in monotherapy.

In a placebo-controlled, double-blind, 24-week Phase 3 monotherapy study, edema-related events were reported in 8.1%, 11.4%, and 7.8% of subjects treated with muraglitazar 2.5 mg, muraglitazaer 5 mg and placebo-treated subjects, respectively. Across all 24-week controlled clinical studies that studied muraglitazar 2.5 mg and 5 mg doses, muraglitazar-treated subjects in combination therapy studies with metformin or sulfonylurea reported edema with an incidence broadly in line with rates seen in the

monotherapy study. In an active-controlled combination study of muraglitazar versus pioglitazone on a background of metformin, the incidence of edema at 24 weeks was 9.2% for muraglitazar 5 mg and 7.2% for pioglitazone 30 mg. It should be noted that the glycemic and lipid efficacy of muraglitazar was also greater than pioglitazone at these doses. Most of these edema-related events were considered mild or moderate in intensity and few subjects discontinued treatment due to this adverse experience.

The mean weight gain observed in 24-week Phase 3 studies with muraglitazar was between 1.1 kg to 4.3 kg. In the active-controlled metformin combination study of muraglitazar 5 mg versus pioglitazone 30 mg in addition to metformin, the mean weight gain at 24 weeks was 1.4 and 0.6 kg from baseline, respectively. In the combination study with SU, mean weight gain from baseline was greater (2.7 kg for 2.5 mg and 4.3 kg for 5 mg vs 0.4 kg for placebo), presumably due to increased endogenous insulin levels associated with administration of a SU.

Hypoglycemic events were reported in < 1% of subjects in all other studies not involving concomitant treatment with a SU. In the placebo-controlled combination study with a SU, confirmed hypoglycemia (documented by symptoms such as dizziness, shakiness, sweating, hunger, and a finger stick blood glucose measurement ≤ 50 mg/dL) was, as expected, reported in more subjects treated with muraglitazar and SU than with SU alone. This finding was associatated with greater glycemic efficacy for subjects treated with the combination then with SU alone

Heart failure adverse events were monitored closely during the muraglitazar clinical program. The clinical presentations, underlying risk factors, management and outcome of heart failure events were in line with the clinical experience gained with the TZDs pioglitazone and rosiglitazone over the past several years.[42] Across all 24-week controlled clinical studies that studied muraglitazar 2.5 mg and 5 mg doses, seven adverse events of heart failure were reported by investigators, yielding incidence rates of 0.19% (1/535), 0.34% (5/1453), and 0.17% (1/572) for subjects on muraglitazar 2.5 mg, muraglitazar 5 mg, and pioglitazone 30 mg, respectively. Although the incidence rates of heart failure events demonstrated a dose relationship trend through the full dose range studied, which included the higher 10 mg and 20 mg doses studied in Phase 2, it is apparent that the propensity to experience a heart failure event depended on underlying CV risk factors. Such risk factors included prior cardiovascular disease history, including

prior heart failure. These same underlying CV disease features have also been associated with events of heart failure in type 2 diabetes subjects treated with the TZDs pioglitazone or rosiglitazone.[43] Overall, for muraglitazar, heart failure cases were of mild to moderate severity and most events resolved within days after administration of diuretics and study drug discontinuation.

Prior to the initiation of the Phase 3 studies, an independent adjudication committee that was blinded to treatment allocation was established to retrospectively review investigator-reported events that could represent heart failure in order to ensure that no events of heart failure, especially serious heart failure events, were overlooked. This assessment referred all events of heart failure and related terms (e.g., dyspnea) and all edema or edema-related events of moderate or greater intensity for independent adjudication. Overall, this adjudication process confirmed nearly all cases of heart failure diagnosed by the study investigators and identified other events as possible early or unrecognized sub-clinical heart failure events, aided in part by elevated B-type natriurietic peptide (BNP) assay measurements that were not available to the investigators. Despite not being diagnosed by the investigators, all adjudicated heart failure events were managed appropriately with no new serious heart failure events being identified. Details of this assessment are described more fully in Section 8.4.7.2.

In general, heart failure events, whether diagnosed by the study investigators or adjudicated retrospectively, were treated and managed effectively. Both diagnosed and adjudicated heart failure events responded to diuretics or other therapies, sometimes without the need to discontinue muraglitazar. Thus, heart failure that occurred in type 2 diabetes subjects treated with muraglitazar was manageable and reversible regardless of whether the events were diagnosed as heart failure or identified by the Adjudication Committee as a symptomatic event such as dyspnea or an edema-related event.

In conjunction with the effects of PPARγ agonism on fluid retention and edema, muraglitazar may also cause dose-related decreases in hemoglobin and hematocrit. These changes may be related to increased plasma volume associated with muraglitazar therapy. Across all diabetes clinical studies, the mean change was -0.57 g/dL in hemoglobin and -0.89% in hematocrit in subjects treated with muraglitazar 5 mg. These changes generally occurred within the first 2 to 8 weeks of therapy and remained stable thereafter. These

changes have rarely been associated with any significant hematologic clinical effects; anemia was reported in < 1% of subjects treated with muraglitazar.

During clinical studies in subjects with type 2 diabetes, 12 of 2895 (0.4%) subjects treated with muraglitazar had alanine transaminase (ALT) values > 3 times the upper limit of normal (ULN) during treatment. All subjects with follow-up values demonstrated reversal of these ALT elevations. Two subjects with elevations in ALT and bilirubin were diagnosed with acute cholecystitis; both were on muraglitazar. Both subjects had resolution of the liver function tests after treatment. There was no increased incidence of cholelithiasis observed with muraglitazar therapy.

During required laboratory testing in clinical studies, sporadic, transient elevations in CK levels were observed. An elevation to greater than 10 times the upper limit of normal was noted in 2 out of 852 (0.23%) muraglitazar subjects who received a statin and in 12 out of 2067 (0.58%) muraglitazar subjects who did not receive a statin. These incidences were not different to those observed in controls. None of these events was associated with muscle related symptoms. There was 1 case diagnosed as rhabdomyolysis by the on-site investigator, based in part on a finding of myoglobinuria, which occurred in an asymptomatic male patient following strenuous exercise and whose CK values returned to near baseline before muraglitazar treatment was stopped. All CK elevations resolved without clinical sequelae.

More details of the clinical safety of muraglitazar are provided in Sections 6, 8 and 9.

2.3.4 Overall Benefit Risk Assessment and Dosing Considerations

Both the muraglitazar 2.5 mg and 5 mg doses were used as starting doses in parallel arm studies for the Phase 3 clinical development program. Efficacy results in both monotherapy and combination therapy demonstrated that the 5 mg dose will enable a greater percentage of subjects to achieve A1C goals and optimum glycemic control. Even at high baseline A1C levels > 10%, muraglitazar 5 mg provided robust glycemic efficacy, reducing A1C in many subjects towards or below target A1C goals. The 5 mg dose also provided greater mean TG lowering and HDL-C elevating benefits relative to the 2.5 mg dose. Thus, the 5 mg dose provided substantial additional benefit relative to the 2.5 mg dose, with more subjects able to achieve both glycemic and lipid treatment goals at the

higher dose. These degrees of glycemic and lipid efficacy, achieved with the muraglitazar 2.5 mg and 5 mg doses, should ultimately result in clinically meaningful microvascular and macrovascular morbidity and mortality benefit for type 2 diabetes patients if results of landmark diabetes and cardiovascular outcomes trials can be extrapolated from the magnitude of A1C and lipid improvements achieved in the muraglitazar clinical program.

Well recognized side effects associated with the TZD PPARγ agonists were also observed with muraglitazar.[18] Thus, the profile of adverse events observed with muraglitazar was generally similar to that of the active comparator pioglitazone.[30,31,32] As with the TZDs, the incidence of specific events was generally related to dose.

Muraglitazar also possesses PPARα agonist activity, but no evidence for a signal of myotoxicity, epatobiliary toxicity (including excess gallstone formation) or nephrotoxicity. This experience includes data on subjects who were concurrently treated with statins, which comprised up to 24% of the type 2 diabetes subjects studied in the muraglitazar combination studies.

Although events related to fluid retention (e.g., edema), as well as the infrequent events of heart failure occurred more often on the 5 mg dose relative to the 2.5 mg dose, the qualitative safety and tolerability profiles for these 2 doses were similar overall. In particular, across all five clinical trials involving monotherapy and combination therapy in subjects with type 2 diabetes, the precipitation or exacerbation of heart failure events was qualitatively similar regardless of dose, including the events observed in subjects randomized to 10 or 20 mg of muraglitazar in the Phase 2 dose-ranging study. Importantly, an evaluation of underlying cardiac and other risk factors prevalent among the type 2 diabetes population in the muraglitazar clinical program indicates that the risk for presenting with a heart failure diagnosis (investigator-reported or adjudicated) depended both on the dose of muraglitazar used and on the presence of underlying cardiac risk factors (i.e., those likely to increase risk for heart failure).

Therefore, both muraglitazar 2.5 mg and 5 mg are recommended as potential alternative starting doses, albeit with important distinctions. Muraglitazar 2.5 mg will represent an appropriate starting dose for subjects with mild degrees of hyperglycemia. The muraglitazar 2.5 mg dose is also the appropriate dose in subjects suspected to be less tolerant to fluid overload, such as subjects with New York Heart Association (NYHA)

Class II heart failure or possibly other significant risk factors for heart failure. Given overall benefit/risk considerations, muraglitazar 5 mg represents a more suitable starting dose choice for markedly hyperglycemic and/or hyperlipidemic diabetes subjects requiring greater initial glycemic and diabetic dyslipidemia efficacy.

In conclusion, muraglitazar will be an important addition to the current therapies available to treat subjects with type 2 diabetes. The clinical development program has shown that muraglitazar has a robust and dose-dependent beneficial effect on the glycemic and lipid profile of subjects with type 2 diabetes. The overall glycemic efficacy and safety profile of muraglitazar supports its use in many patients with type 2 diabetes, both as monotherapy and in combination therapy. In addition, because approximately two thirds of type 2 diabetes patients have untreated dyslipidemia in addition to hyperglycemia, muraglitazar's overall favorable profile on improving HDL-C, TG, and LDL particle size aspects of dyslipidemia supports the use of muraglitazar in diabetic patients with these abnormalities. Muraglitazar is also durable and improves a series of other CV risk biomarkers, and further investigation of muraglitazar's long-term clinical outcome benefits in patients with diabetes and/or metabolic abnormalities that are at increased risk for CV disease will clearly be instructive. Overall, the control that muraglitazar provides for both hyperglycemia and dyslipidemia, with a choice of doses and the option of titration, allows physicians to treat a wide range of patients with type 2 diabetes very effectively.

More detailed discussion of the risk benefit assessment and dosing considerations can be found in Section 12.

2.4 Proposed Labeling for Muraglitazar

It is proposed that muraglitazar be indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Muraglitazar should be indicated for use as monotherapy and also for use in combination with metformin or a sulfonylurea when diet, exercise, and 1 of these agents alone does not result in adequate glycemic control. For patients inadequately controlled with metformin or a sulfonylurea, muraglitazar should be added to, rather than substituted for, metformin or a sulfonylurea. Given its underlying dual PPARγ and PPARα pharmacology, the efficacy of

muraglitazar to improve components of diabetic dyslipidemia in patients with type 2 diabetes is also proposed to be highlighted.

In recommended labeling, muraglitazar will not be indicated in patients with NYHA III and IV heart failure. Because the following patient populations have not been studied in this development program, they will not be indicated for use of muraglitazar in the initial label: patients with NYHA Class III and IV heart failure, patients using insulin, and patients less than 18 years old.

3 OVERVIEW OF THE DEVELOPMENT PROGRAM FOR MURAGLITAZAR

The combined non-clinical and clinical development program for muraglitazar is very extensive and has been guided by several strategic approaches.

1) For non-clinical toxicology, known animal toxicology and carcinogenicity findings for other PPAR agonists active at all three (γ, α, and δ) receptor isoforms led to the design and implementation of an extensive program, with dosing at high multiples in several species and with thorough investigative and mechanistic toxicological experiments for findings of potential significance in patients, such as for bladder cancer.

Consequently, the toxicity of muraglitazar in animals was characterized in a comprehensive nonclinical toxicology program. Single-dose oral toxicity studies were conducted in mice, rats, and monkeys while repeat-dose toxicity studies were completed in dogs, rats, and monkeys lasting up to 1, 6 and 12 months in duration, respectively. Muraglitazar was also assessed in a battery of in vitro and in vivo genetic toxicity studies; in carcinogenicity studies in mice and rats; in reproductive and developmental toxicity studies in rats and rabbits; in in vitro and in vivo ocular and dermal irritation and contact allergenic studies; in immunotoxicologic evaluation in rats; and in phototoxicity evaluation in mice. Supplemental investigative toxicology and carcinogenicity mechanism studies in rats and dogs were done. Additional toxicity studies were conducted as appropriate, to assist in dose selection for the definitive studies.

2) For clinical testing and development, clinical experience with TZD PPAR agonists active at the γ and α receptor isoforms led to the design and implementation of a large, dose-ranging Phase 2 clinical trial, which allowed a thorough investigation of a full range of doses. As will be seen, it yielded a progressive dose range for efficacy and a clear threshold for edema and infrequent heart failure events. This result was critical in guiding the choice of starting doses for the Phase 3 program.

3) The muraglitazar Phase 3 clinical program included an informative active comparator study assessing the higher 5 mg Phase 3 dose against the highest dose of pioglitazone (30 mg) recommended for use in combination with metformin at the time this study was conducted. As will be seen, this study and the other Phase 3 placebo-controlled studies with muraglitazar as monotherapy and in combination have provided a thorough understanding of benefit and risk and guided labeling and dosing recommendations for muraglitazar.

4) Finally, long-term extensions, including an extension of the Phase 2 study at doses above those that were progressed in Phase 3 development, were conducted. Once again, as will be seen, this approach has provided important efficacy durability data and an extensive safety experience, including up to 18 months with a dose that is 4-fold higher than the highest dose put forward in this NDA.

Thus, the overall clinical development program for muraglitazar was also comprehensive, and includes Phase 1, Phase 2 and Phase 3 studies as monotherapy or combination therapy with other antihyperglycemic agents (Figure 3.1). The Clinical Pharmacology program evaluated the pharmacokinetics of muraglitazar in 22 Phase 1 and Phase 2a studies, including 20 studies conducted in healthy subjects, 1 study in subjects with hepatic dysfunction, and 1 study in subjects with type 2 diabetes. The pharmacokinetics of muraglitazar was assessed in relation to age, gender, and hepatic impairment. In addition, a population pharmacokinetic analysis has been performed.

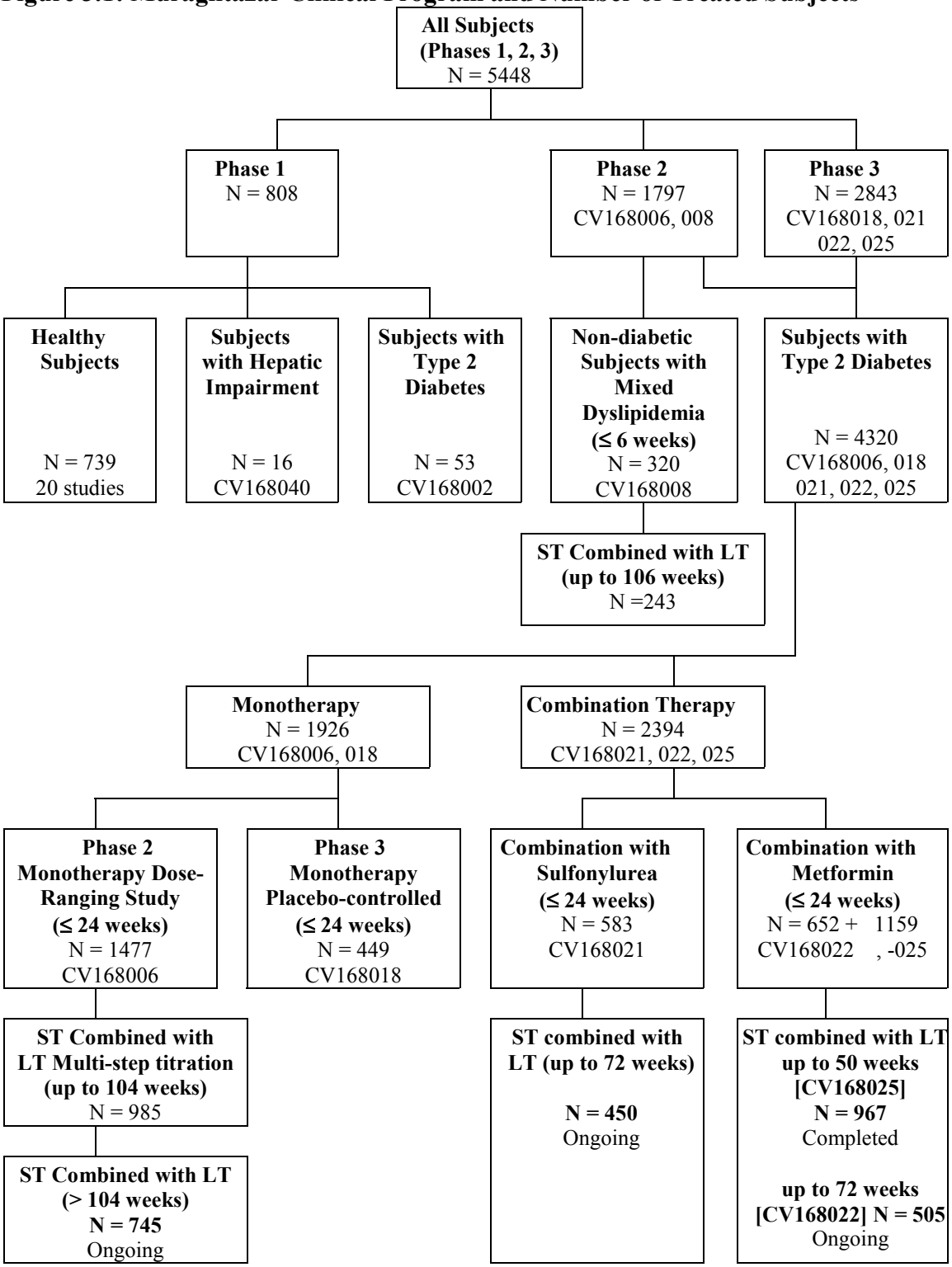
The Phase 2/3 worldwide muraglitazar clinical development program included 6 studies in 4640 treated subjects, 3226 of whom received muraglitazar, 823 received pioglitazone, and 591 received placebo. Five of the 6 studies included 4320 subjects with type 2 diabetes: 2 of these studies (CV168006 and CV168018) evaluated muraglitazar

monotherapy in subjects who had inadequate glycemic control with diet and exercise and 3 studies (CV168021, CV168022, and CV168025) evaluated muraglitazar in combination with glyburide or metformin in subjects who had inadequate glycemic control on either a sulfonylurea or metformin alone. All of the 5 studies in subjects with type 2 diabetes had a short-term (ST), 24-week phase for assessment of glycemic control. In addition, 4 of the 5 studies have long-term (LT) phases, CV168006, CV168021, CV168022, which are currently on-going and CV168025, which has concluded.

Additionally, 1 study (CV168008) included 320 non-diabetic subjects with mixed dyslipidemia and had a ST duration phase of 6 weeks and a LT phase of 106 weeks (including the ST phase). Both of these phases are completed and were reported in the NDA. A synopsis of each of these 2 study phases is attached to this document in Attachments 3.1A and 3.1B.

The NDA (including the 120-day Safety Update) currently under review by the FDA includes the ST phases from all 6 studies as well as at least 2-year data in 849 muraglitazar-treated subjects from 2 of the studies (interim data for CV168006 and final data for CV168008). Long-term data (50 weeks) recently available from the CV168025 study as well as LT data from CV168021 and CV168022 have been included in this document in the Complete Dataset analyses.

Figure 3.1: Muraglitazar Clinical Program and Number of Treated Subjects



4 NONCLINICAL TOXICOLOGY

4.1 Toxicology Overview

Muraglitazar demonstrated a low order of acute toxicity with minimum lethal oral doses greater than 1000 mg/kg in mice and monkeys and greater than 4000 mg/kg in rats. Muraglitazar was generally well tolerated in repeat-dose studies in mice, rats, and monkeys at doses resulting in AUC exposures 12, 53, and 9 times, respectively, clinical exposure at 5 mg. The majority of drug-related findings in repeat-dose toxicity studies were pharmacologically mediated and similar to those observed with marketed PPARγ agonists. Muraglitazar was not hepatotoxic, myotoxic, nephrotoxic, or cardiotoxic in rats or monkeys at exposures up to 376 and 59 times, respectively, that in humans at 5 mg. Muraglitazar was not mutagenic or clastogenic in the standard battery of in vitro and in vivo genotoxicity studies. Importantly, human Phase I metabolites were also assessed for their genotoxic potential since they were formed in the in vitro genotoxicity studies of muraglitazar using S-9 metabolic activation. Muraglitazar was not teratogenic at maternal exposures up to 5 (rabbit) and 406 (rat) times human exposure at 5 mg and adversely affected reproductive function in female rats only at an overtly toxic, clinically nonrelevant dose (exposure ≥ 228 times clinical exposure). Key results from the cardiovascular safety, rodent carcinogenicity, and relevant tumor mechanistic studies completed with muraglitazar are provided below.

Nonclinical Cardiovascular Safety

- Muraglitazar was assessed for its potential to produce cardiovascular effects in routine safety pharmacology and toxicity studies. Muraglitazar demonstrated an excellent cardiovascular safety profile, and key observations from the nonclinical studies are as follows:
- In the in vitro hERG and Purkinje fiber assays, muraglitazar demonstrated minimal to no cardiac liability at concentrations greatly exceeding clinical exposure (≥ 220 times free drug concentrations at 5 mg).
- In a single-dose intravenous cardiovascular safety pharmacology study in telemetered dogs, there were no electrocardiogram (ECG) changes, but a reversible minimal decrease in blood pressure was observed at muraglitazar exposures ≥ 120 times that in humans at 5 mg.

- In repeat-dose studies in monkeys, there were no ECG changes at muraglitazar exposures up to 68 times human exposure for 4 months and up to 44 times human exposure for 1 year. Minimal decreases in blood pressure occurred at muraglitazar exposures 53 times human exposure at 5 mg.
- In rats treated for 1 to 6 months, heart weights were increased at muraglitazar exposures ≥ 53 times those in humans and after 6 months of treatment were accompanied, microscopically, by minimal to mild myocardial hypertrophy and generalized edema only at the overtly toxic dose of 300 mg/kg (≥ 312 times clinical exposure at 5 mg).
- In monkeys treated for 9 to 12 months, heart weights were increased and after 12 months of treatment were accompanied by echocardiographic changes (increased thickness of the left ventricular wall during diastole and systole and an increase in the calculated shortening fraction due to a decrease in the systolic left ventricular chamber diameter) at muraglitazar exposures at least 44 times human exposure at 5 mg. Similar effects were not present at 17 times human exposure.
- In monkeys administered muraglitazar for up to 12 months, persistent subcutaneous edema was observed at muraglitazar exposures 9 to 68 times human exposure at 5 mg. A few occurrences of edema were noted at muraglitazar exposures 2 times those in humans at 5 mg.

The no-effect doses for cardiac changes in rats and monkeys resulted in muraglitazar exposures 8 and 17 times, respectively, the human exposure at 5 mg.

4.2 Carcinogenicity

The carcinogenic potential of muraglitazar was evaluated in lifetime studies conducted in mice at doses of 0, 1, 5, 20, and 40 mg/kg/day and in rats at doses of 0, 1, 5, 30, and 50 mg/kg/day. Key observations from these studies are as follows:

- In mice, there were no statistically significant positive trends in tumor incidence. However, low incidences of benign gallbladder adenomas (1/38 and 2/32) occurred in male mice at the 2 highest dose levels and were considered drug related because focal mucosal hyperplasia of the gallbladder was noted in males at all doses and in females at the 3 highest dose levels. Exposures to muraglitazar at the 2 doses associated with gallbladder adenomas in male mice were approximately 62 and 141 times human exposure at 5 mg. Exposure at the highest nontumorigenic dose of 5 mg/kg in male mice was 17 times human exposure at 5 mg. No proliferative changes were noted in

the biliary tree of rats or gallbladder of dogs and monkeys at exposures up to 376, 101, and 59 times, respectively, human exposure at 5 mg.

- In rats, the incidences of subcutaneous liposarcoma and subcutaneous benign lipoma were increased in male and female rats, respectively, at the high dose of 50 mg/kg with exposures 48 and 59 times human exposure at 5 mg in male and female rats, respectively. At the highest nontumorigenic dose, exposures to muraglitazar were 37 times (males) and 45 times (females) human exposure at 5 mg. The adipocyte tumorigenic response in rats was considered pharmacologically mediated and due to prolonged and persistent over stimulation of adipocytes at high systemic exposures to drug.
- In male rats, the incidences of transitional cell papilloma and carcinoma of the urinary bladder were increased at the 3 highest dose levels. In addition, the incidence of urothelial hyperplasia of the urinary bladder was increased in males at doses of 5 mg/kg or greater and in females at 30 and 50 mg/kg. Proliferative lesions were not observed in the renal pelvis. The bladder tumors were associated with increased urinary levels of calcium and magnesium-containing precipitates, crystals, aggregates, and/or calculi. Systemic exposure at the lowest tumorigenic dose in male rats was 8 times that observed in humans at 5 mg. At the highest doses not producing an increased incidence of urinary bladder tumors in male and female rats, systemic exposures were approximately 1.3 and 59 times, respectively, the human exposure at 5 mg. There were no urinary bladder proliferative lesions observed in the carcinogenicity study in mice at exposures up to 154 times human exposure at 5 mg or cytotoxic, proliferative, or inflammatory changes in the urinary bladder mucosa of monkeys treated for 9 months to 1 year at exposures up to 59 times that in humans.

The urinary bladder tumorigenic response in male rats is distinguished from the other tumor findings by the relatively low exposures at which tumors were observed and by the low safety margin (1.3 times human exposure at 5 mg) at the nontumorigenic dose. Therefore, investigative studies were initiated to determine the mode of tumor development. Although the investigative studies were designed to assess both direct and indirect modes of tumor development, an indirect mode involving mucosal injury and proliferation secondary to increased urinary solids was the most plausible explanation to account for the male-rat specificity of the response since male rats are predisposed to urolithiasis compared to female rats and male and female mice. Moreover, urolithiasis is a well recognized non-genotoxic mechanism of urinary bladder carcinogenesis in rats, particularly male rats,[35] that has been documented or purported for a diverse list of

agents, including certain marketed sulfonamides, carbonic anhydrase inhibitors, and the PPARγ agonist, pioglitazone.

In the investigative studies with muraglitazar, special techniques were employed for urine sampling, specimen preparation, and urine sediment and mucosal evaluations to optimize the detection and characterization of diurnal variations in urine solids and dose- and time-dependent effects in urine composition and mucosal morphology. Key findings from the investigative studies with muraglitazar conducted at nontumorigenic (1 mg/kg/day) and tumorigenic (50 mg/kg/day) doses are highlighted below:

- Persistence of urine pH ≥ 6.5 in treated male rats on normal diet, which favors formation of calcium- and magnesium-containing precipitates, crystals, and calculi in the presence of prolithogenic changes in other urine constituents.
- Sustained decreases in urine soluble calcium-to-creatinine and phosphate-to-creatinine ratios in the presence of unaltered total calcium-to-creatinine ratios at the tumorigenic dose in male rats on normal diet which collectively indicate increased calcium phosphate solids in urine; this effect was present during the early light phase when contact of cytotoxic calcium phosphate precipitates with the ventral bladder mucosa would be facilitated by the force of gravity during a period of reduced activity and urination while the animal sleeps.
- Sustained dose- and time-dependent reductions in urine citrate, a major chelator of calcium and magnesium in urine, and an inhibitor of the formation, growth, and aggregation of calcium and magnesium salt crystals.
- Dose-related increased calcium phosphate precipitate, calcium phosphate crystals and calculi, magnesium ammonium phosphate crystals and aggregates, and calcium oxalate-containing thin rod-like crystals in urine sediment of treated rats in association with the urothelial cytotoxic and proliferative responses and prior to tumor development.
- In male rats, dose- and time-dependent focal to locally extensive necrosis and associated regenerative hyperplasia of the bladder mucosa [as determined by bromodeoxyuridine (BrdU) labeling, light microscopy and scanning microscopy] with a lesion predilection for the ventral (dependent) regions of the bladder after ≥ 3 months of treatment.
- Proximity of mucosal deposits of calcium phosphate precipitate to areas of mucosal cytotoxicity and proliferation at 3, 6, and 9 months.
- No evidence of a cytotoxic or proliferative mucosal response in the urinary bladder of female rats after 3 months even though systemic exposures to muraglitazar were similar to those in males.

- Progression of focal simple mucosal hyperplasia at 3 months to nodular hyperplasia by 6 months and transitional cell tumors by 9 months in high-dose male rats.
- As noted for the cytotoxic and hyperplastic mucosal changes, urinary bladder masses were localized on the ventral to anterioventral (dome) regions of the mucosa rather than randomly.
- Urinary acidification via dietary supplementation with 1% ammonium chloride completely inhibited the mucosal cytotoxic, proliferative, and tumorigenic responses (see Table 4.2) in male rats treated for up to 15 months without altering background rates of mucosal proliferation or urinary and plasma drug levels. (Note: urine acidification inhibits formation of calcium- and magnesium-containing precipitates and crystals in rats.)

Table 4.2: Incidence of Urinary Bladder Proliferative Lesions in Male Rats Treated with Muraglitazar for up to 15 Months

Diet:	Normal			Acidified		
Dose (mg/kg):	**0**	**1**	**50**	**0**	**1**	**50**
No. Examined (Months 6 - 15):	59	60	75[a]	54	56	63
Transitional Cell Hyperplasia	2	5	34	1	0	0
Transitional Cell Papilloma	0	0	3	0	0	0
Transitional Cell Carcinoma	0	1	19	0	0	0

[a] Higher number of rats examined because of premature deaths from urinary bladder tumors.

There is no evidence from studies with muraglitazar for a direct pharmacologically based mechanism involving trophic PPAR stimulation of urothelium based on the following key points:

- PPARγ transactivation by a selective agonist in vitro facilitates differentiation rather than proliferation of human urothelium.[36]
- Mucosal PPAR α/γ expression patterns are similar in dorsal and ventral urinary bladder of male and female rats, whereas the tumorigenic response is regiospecific and male rat specific.
- There were higher systemic drug exposures, but no associated urinary bladder tumors in female rats and male and female mice when compared to male rats in the oral carcinogenicity studies.

- Urinary bladder tissue concentrations of muraglitazar and its metabolites were similar in male and female rats.
- Urine levels of muraglitazar and its metabolites in rats represent less than 5% of an administered dose and in females at 50 mg/kg exceed considerably those in males at 5 mg/kg (the lowest tumorigenic doses in males).
- In studies with monkeys, a species demonstrating similar in vitro PPAR α/γ transactivation potential to humans, there was no evidence of urinary bladder proliferative changes after 9 or 12 months of treatment at exposures up to 59 times those in humans at 5 mg.

When considered collectively, results from the carcinogenicity studies and relevant investigative studies support that the mode of urinary bladder tumorigenesis involves muraglitazar-related alterations in urine composition that predispose to urolithiasis. The increased urinary precipitates, crystals, and calculi result in localized rather than diffuse mucosal injury (necrosis) with primarily an apical (anterioventral) to ventral bladder distribution as a consequence of physical irritation induced during micturition and from contact of large amounts of cytotoxic calcium phosphate precipitate with the ventral bladder mucosa due to the force of gravity. Moreover, calcium phosphate precipitate (when phagocytosed) has been shown to stimulate mitogenesis in vitro [37] and reduced soluble calcium concentrations (hypocalciuria), as noted in this study, may elicit a pro-mitogenic or dedifferentiating effect on basal epithelium at sites of injury, based on results observed in rat urinary bladder explants.[38] Chronic mucosal cytotoxicity and the associated regenerative hyperplasia increase the likelihood for fixation of spontaneous mutations and thereby predispose to the development of urinary bladder tumors.

Results of the rodent carcinogenicity and relevant mechanistic studies do not indicate that muraglitazar poses a carcinogenicity risk to humans at clinical doses and exposures.

Results of the rodent carcinogenicity and relevant mechanistic studies do not indicate that muraglitazar poses a carcinogenicity risk to humans at clinical doses and exposures. Key points supporting this conclusion follow:

- The urinary bladder tumorigenic response was male-rat specific even though exposures to drug were higher in female rats and male and female mice. Moreover, there were no cytotoxic, proliferative, or inflammatory changes in the urinary bladder

mucosa of monkeys treated for 9 to 12 months at exposures up to 59 times that in humans at 5 mg.

- There was no apparent association between muraglitazar treatment and the formation of any type of urinary crystal in Phase 3 clinical trials.
- There is no evidence suggesting the presence of microcrystals of any source in human urine is irritating to the urinary bladder mucosa. Moreover, crystalluria has not been established as a risk factor for urinary bladder cancer in humans. A potential outcome of reduced urinary levels of citrate or other causes of crystalluria in humans is nephrolithiasis or ureterolithiasis, which can result in acute pain and the need for medical or surgical intervention.
- Urinary bladder tumors resulted from pharmacologically-mediated alterations in urine composition that predispose to crystalluria and consequent mucosal irritation in rats, particularly male rats. A panel of rodent carcinogenicity experts reached a similar conclusion based on their independent review of the preclinical investigative data for muraglitazar (See Expert Commentary, Attachment 4.2)
- The high-dose tumors in rodents (gallbladder adenomas in male mice and subcutaneous adipocyte tumors in rats) occurred by a nongenotoxic mode of action at exposures ≥ 48 times human exposure at 5 mg and were characterized by large safety margins at the highest nontumorigenic dose (≥ 17 times human exposure at 5 mg).
- The rodent tumorigenic profile of muraglitazar was similar to that noted collectively for the marketed PPARγ agonists, pioglitazone and rosiglitazone, in that urinary bladder tumors in male rats and adipocyte tumors in male and female rats were the principal tumor findings. Moreover, at comparable mg/m^2 or exposure multiples of the highest recommended clinical dose, only 1 tumor type was observed with each agent, including muraglitazar.

5 HUMAN PHARMACOKINETICS

The general pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of muraglitazar have been investigated in 20 clinical pharmacology studies in the US and 2 studies in Japan. These comprised 18 studies in healthy subjects in the US and 2 in Japan, 1 Phase 2a PK/PD study in subjects with type 2 diabetes, and 1 PK study in subjects with stable hepatic impairment (Table 5). In addition, population pharmacokinetic analysis results are presented from the Phase 2a study and a Phase 3 study (CV168018) in type 2 diabetic subjects (see Attachment 5).

Table 5: Outline of Clinical Pharmacology Studies of Muraglitazar

STUDY TYPE	STUDY NUMBER(S)
Safety and Pharmacokinetics in Healthy Subjects	
Single-Dose Administration	CV168001
Multiple-Dose Administration	CV168004
ADME	CV168007, CV168041
Pharmacokinetics and Pharmacodynamics in Type 2 Diabetic Subjects	
Multiple-Dose Administration	CV168002
Pharmacokinetics in Special Populations	
Age-Gender	CV168010
Single-Dose Administration in Japanese Subjects	CV168009
Multiple-Dose Administration in Japanese Subjects	CV168027
Hepatic Insufficiency	CV168040
Bioavailability Studies	
Relative Bioavailability	CV168014
Food Effect	CV168003, CV168011
Drug Interaction Studies	
Warfarin	CV168003
Pravastatin	CV168012
Glyburide	CV168013
Simvastatin	CV168015
Gemfibrozil	CV168037
Metformin	CV168039
Atorvastatin	CV168044
Fenofibrate	CV168046
Ketoconazole	CV168047
Famotidine	CV168060
Thorough ECG Evaluation	
Multiple-Dose ECG Study	CV168043

Muraglitazar has a consistent and predictable PK profile which has been characterized in healthy subjects and in subjects with type 2 diabetes. Muraglitazar has a low potential for interactions with food or concomitantly administered drugs. After oral administration, muraglitazar is rapidly absorbed with plasma concentrations detectable within 30 minutes and peak plasma concentrations observed between 0.5 to 6 hours for the 5 mg dose. Administration of muraglitazar with a high fat meal or with an agent that increases gastric pH (famotidine) did not affect overall muraglitazar exposure (AUC). Plasma concentrations of muraglitazar increased in a dose-proportional manner over and beyond the therapeutic dose range (up to 20 mg). Muraglitazar elimination half-life is approximately 24 hours (range, 19 to 31 hours). Muraglitazar is extensively metabolized through both Phase 1 and Phase 2 pathways. The major biotransformation pathways are glucuronidation, hydroxylation, O-demethylation, and isoxazole ring opening. The parent compound contributes the majority (~76%) of the drug-related plasma exposure. There are no known major circulating metabolites of muraglitazar with pharmacologic activity. Muraglitazar is primarily eliminated via the biliary pathway as unchanged muraglitazar, metabolites and conjugates. Muraglitazar has negligible renal elimination.

Muraglitazar PK is similar in type 2 diabetic subjects when compared to healthy subjects. In healthy elderly vs young subjects, as well as male vs female subjects, there were no clinically significant differences in muraglitazar PK. In a clinical study of subjects with type 2 diabetes, population pharmacokinetic analyses indicated that the pharmacokinetics of muraglitazar are not influenced by age, body weight, race, or gender. Moderate or severe hepatic impairment resulted in a 2- to 3-fold increase in muraglitazar AUC when compared to matched healthy subjects.

Muraglitazar is a substrate for multiple CYP450 isoenzymes in humans including CYP3A4, 2C19, 2C9, 2C8 and 2D6, reducing the probability of significant drug-drug interaction. Clinical studies with inhibitors of CYP3A4 (ketoconazole) and 2C8 (gemfibrozil) found only small increases in muraglitazar maximal drug concentration (Cmax) (23 to 27%) or AUC (23 to 46%) that are not considered to be clinically relevant. Muraglitazar did not affect the pharmacokinetic profile of a number of drugs, including substrates of CYP2C9 (S-warfarin), 2C19 (R-warfarin), and 3A4 (atorvastatin or simvastatin) or frequently-used antidiabetic or lipid-lowering agents such as metformin, pravastatin, and fenofibrate.

5.1 QTc Study

The effect of muraglitazar on the QT interval corrected (QTc) was evaluated in an intensive ECG study in healthy subjects. The main objective was to determine the effect of multiple-dose muraglitazar on the QT interval corrected by the Fridericia method (QTcF). This double-blind, placebo-controlled study included a positive control (moxifloxacin), and cross-over design with multiple-dose administration of muraglitazar 5 mg or 50 mg for 8 days. Moxifloxacin prolonged QTcF by 16.6 msec more than placebo with a lower 95% confidence interval of 14.1 msec. In contrast, muraglitazar did not result in significant changes in QTcF compared to placebo at either dose (-0.44 msec for 5 mg and 3.9 msec for 50 mg) with upper 95% confidence intervals (2.35 msec for 5 mg and 6.67 msec for 50 mg) that were below the a priori criteria for a positive effect specified in the protocol.

Additional discussion of the results from these studies can be found in Attachment 5.

6 OVERVIEW OF CLINICAL STUDIES AND RATIONALE FOR DOSE SELECTION

The dose-ranging study CV168006 was the initial pivotal study of the clinical development program for muraglitazar. It was designed to explore a 40-fold range of doses (including a "mock" placebo dose which consisted of muraglitazar 0.5 mg daily) over 24 weeks duration of treatment in a large population of type 2 diabetes subjects in order to fully characterize efficacy and safety/tolerability before additional pivotal Phase 3 studies were conducted. The selection of more active Phase 2 daily doses for muraglitazar (1.5 mg, 5 mg, 10 mg and 20 mg) was based on fasting and mean daily glucose (MDG) concentration changes in a multiple ascending dose clinical trial treating type 2 diabetes subjects for 24 weeks duration. During the first 24 weeks of treatment in this dose-ranging study, subjects were evaluated for changes in MDG levels at periodic intervals. If protocol-defined criteria for MDG levels were not met, blinded dose titration up to the next higher dose allowed for in the protocol was undertaken, ensuring that subjects were not left on an ineffective dose such as 0.5 mg muraglitazar for very long. This Phase 2 trial included a blinded arm with a daily dose of pioglitazone 15 mg, which could be titrated in 1 step to 45 mg as needed to maintain glycemic control. Dose titration

was referred to as the "rescue" therapy phase in the protocol, and was only allowed once per subject during the ST phase.

The following sections describe the results of the Phase 2 dose-ranging study and address how these results informed muraglitazar dose choices for Phase 3 trials.

6.1 Statistical Methods

The analysis of the primary endpoint, i.e. change from baseline in A1C to Week 24 was based on an analysis of covariance (ANCOVA) model with treatment group as the effect, and with the baseline value as a covariate. Although preliminary assessments suggested non-normality, the confidence intervals for the treatment means are believed to be robust due to the large sample size. However to be conservative, a non-parametric rank-based ANCOVA model was used to report p-values rather than a parametric test.

The primary comparisons were between each of the 4 muraglitazar treatment arms (1.5 mg, 5 mg, 10 mg, and 20 mg) and the muraglitazar 0.5 mg arm. A sequential testing procedure was used to preserve an overall significance level of 0.05 and each comparison was performed at a two-sided $\alpha = 0.05$ level. Other glycemic and lipid parameters were analyzed using a similar ANCOVA model. Unless otherwise stated all analyses on the efficacy parameters used the last observation carried forward (LOCF) methodology whereby the last post-baseline measurement prior to rescue medication was carried forward.

Subjects included in the efficacy analyses are those randomized, who received at least 1 dose of ST study medication, and who have a baseline value and at least 1 post-baseline measurement for the parameter. In addition, for analyses of A1C only subjects who received treatment for at least 6 weeks were included, to allow enough time to see a change in A1C.

6.2 Efficacy data from Dose-Ranging Study CV168006

Study CV168006 is a Phase 2, randomized, double-blind, active-controlled, 6-arm, parallel-group, dose-ranging study that evaluated the effect of muraglitazar in doses of 0.5 mg, 1.5 mg, 5 mg, 10 mg, and 20 mg and pioglitazone 15 mg in subjects with type 2

diabetes. During the 24-week ST phase, subjects with a lack of glycemic control were eligible to enter a rescue phase. The rescue component allowed subjects that did not meet prespecified glycemic parameters during the ST treatment phase to be titrated once to a higher dose of the drug to which they were randomized. Only the results of the ST phase of this study are described here in Section 6, while the LT results are described in Section 7.7.

6.2.1 A1C - 24-week Data from CV168006

Change from Baseline in A1C at Week 24

Baseline mean A1C ranged from 8.13% to 8.23% for subjects in the muraglitazar dose groups and was 8.31% in the pioglitazone 15 mg group. After 24 weeks of treatment, there was a dose-dependent reduction from baseline in A1C observed for the muraglitazar dose groups (Table 6.2.1A). The mean change from baseline in A1C was -0.25%, -0.57%, -1.18%, -1.52%, and -1.76% for the muraglitazar 0.5 mg, 1.5 mg, 5 mg, 10 mg and 20 mg groups, respectively. For pioglitazone 15 mg the mean change from baseline was -0.57%. There were statistically significant larger mean reductions in A1C for each of the other muraglitazar dose groups compared to the muraglitazar 0.5 mg dose ($p = 0.0008$ for the comparison between muraglitazar 1.5 mg group vs muraglitazar 0.5 mg group and $p < 0.0001$ for the comparisons between the muraglitazar 5 mg, 10 mg, and 20 mg groups vs muraglitazar 0.5 mg group).

Proportion of A1C Responders

At Week 24, muraglitazar produced dose related reductions in A1C and FPG. In addition the proportion of subjects who achieved a therapeutic response (A1C <7% or <6.5%) increased as the dose of muraglitazar increased (Table 6.2.1B). Results for subjects in the pioglitazone 15 mg group were similar to results for subjects in the muraglitazar 1.5 mg group for both levels of response criteria.

Table 6.2.1A: Change from Baseline in A1C at Week 24 LOCF - Each Dose Level of BMS-298585 vs BMS-298585 0.5 mg (ST Phase CV168006)

Measure: A1C Unit: %	BMS 0.5MG N=236	BMS 1.5MG N=259	BMS 5MG N=245	BMS 10MG N=249	BMS 20MG N=237
Summary Statistics					
n	216	235	227	231	227
Baseline Mean (SD)	8.18 (1.06)	8.15 (1.05)	8.23 (1.01)	8.18 (1.05)	8.13 (1.08)
Week 24 LOCF Mean (SD)	7.92 (1.55)	7.59 (1.54)	7.04 (1.37)	6.66 (1.22)	6.38 (1.18)
Mean Change from Bsl. (SD)	-0.25 (1.08)	-0.56 (1.13)	-1.19 (1.12)	-1.52 (1.17)	-1.75 (1.17)
Adjusted Change from Baseline					
Mean (SE)	-0.25 (0.08)	-0.57 (0.07)	-1.18 (0.07)	-1.52 (0.07)	-1.76 (0.07)
95% two-sided CI	[-0.40, -0.11]	[-0.71, -0.42]	[-1.32, -1.03]	[-1.66, -1.38]	[-1.90, -1.61]
Difference in Adjusted Change from Baseline vs BMS 0.5MG					
Mean (SE) (1)		-0.31 (0.10)	-0.92 (0.11)	-1.27 (0.11)	-1.51 (0.11)
Rank p-value (*)		0.0008 *	<.0001 *	<.0001 *	<.0001 *
95% two-sided CI		[-0.52, -0.11]	[-1.13, -0.72]	[-1.47, -1.06]	[-1.71, -1.30]

Source: CSR CV168006ST Table ST 10.1.1A

Dataset: Randomized Subjects
Notes: ANCOVA model: post-pre=pre treatment.
(1) Estimate = Adjusted Mean Change - Adjusted Mean Change for BMS 0.5MG
* Between-group pairwise comparisons significant at alpha=0.05, using Koch-Gansky procedure.

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Table 6.2.1B: Number (Percent) of Subjects Achieving Glycemic Response (A1C) at Week 24 (LOCF) ST Phase CV168006

	Number (%) of Subjects					
	BMS-298585					pioglitazone
	0.5 mg N=236	1.5 mg N=259	5 mg N=245	10 mg N=249	20 mg N=237	15 mg N=251
Number of subjects with available data for A1C:	216	235	227	231	227	230
A1C < 6.5%	31 (14)	56 (24)	87 (38)	120 (52)	152 (67)	49 (21)
A1C < 7%	66 (31)	95 (40)	133 (59)	172 (74)	186 (82)	98 (43)

Dataset: Randomized Subjects

6.2.2 Lipids - 12-week Data from CV168006

In addition to the dose-dependent effect noted on the glycemic parameters, there was also a dose-dependent effect noted on the lipid parameters, with an overall decrease in TG, non-HDL-C and apoB and an increase in HDL-C (Table 6.2.2). Values for free fatty acids (FFAs) are also decreased (Table 6.2.2) Reductions in FFA levels contribute to improvements in insulin sensitivity as well as lipoprotein improvements and, therefore, the FFA results are presented with the glycemic endpoints for the other studies.

Table 6.2.2: Percent Change from Baseline in Lipids at Week 12 (LOCF), Short-term Phase (CV168006)

	Adjusted Mean % Change From Baseline (SE)					
	BMS-298585[a]					pioglitazone[a]
Lipid Parameter	0.5 mg N = 236	1.5 mg N = 259	5 mg N = 245	10 mg N = 249	20 mg N = 237	15 mg N = 251
TG (mg/dL)	-3.74 (2.32)	-6.47 (2.16)	-21.10 (1.89)	-31.71 (1.60)	-40.96 (1.41)	-9.25 (2.11)
HDL-C (mg/dL)	5.87 (1.06)	7.84 (1.03)	17.37 (1.16)	19.85 (1.16)	22.77 (1.21)	10.01 (1.04)
LDL-C (mg/dL)	3.29 (1.41)	-1.67 (1.29)	2.98 (1.40)	-0.06 (1.33)	-7.44 (1.25)	3.18 (1.36)
apoB (mg/dL)	-2.59 (1.50)	-4.98 (1.32)	-9.65 (1.26)	-15.74 (1.15)	-22.05 (1.06)	-4.73 (1.35)
TC (mg/dL)	2.56 (0.92)	0.10 (0.86)	1.09 (0.90)	-1.66 (0.85)	-6.58 (0.83)	1.78 (0.89)
non-HDL-C (mg/dL)	1.54 (1.23)	-2.15 (1.13)	-3.58 (1.15)	-7.92 (1.08)	-15.38 (1.01)	-0.66 (1.16)
apoA_1 (mg/dL)	4.63 (1.26)	6.95 (1.16)	9.20 (1.19)	5.83 (1.12)	4.72 (1.11)	5.98 (1.18)
FFA (mmol/L)	-7.73 (3.40)	-17.48 (2.75)	-26.84 (2.43)	-31.50 (2.24)	-39.45 (1.96)	-15.25 (2.89)

[a] ANCOVA model: log (post)-log (pre) = log (pre) treatment. The results for the BMS-298585 groups are obtained using the ANCOVA model including only BMS-298585 treatment groups whereas the pioglitazone results are obtained using the ANCOVA model with all BMS-298585 treatment groups plus pioglitazone 15 mg group.

Data Set: Randomized Subjects
Source: CSR CV168006ST Table 10.3.1.1

6.3 Safety data from Dose-Ranging Study CV168006

The results of this study also demonstrate that muraglitazar at doses up to 5 mg was well tolerated, with a safety and tolerability profile overall that was comparable to what was observed with pioglitazone 15 mg.

- Review of the safety data revealed no signal for liver or muscle toxicity.
- A dose-dependent increase in weight over time was observed across the entire muraglitazar dose range, especially at doses higher than muraglitazar 5 mg.

- Adverse events of edema were similar between the muraglitazar 5 mg and lower doses and pioglitazone 15 mg; there was a higher incidence of edema-related events in the muraglitazar 10 mg and 20 mg dose groups.
- Events of heart failure were observed at a low frequency only in the muraglitazar 10 mg (2.0%) and 20 mg (0.8%) dose groups.
- Dose-related decreases from baseline in hemoglobin, white blood cell count (WBC) and neutrophils occurred in subjects taking muraglitazar.

Selected events from the dose ranging study CV168006 that were considered along with glycemic and lipid efficacy results to define dose selection for Phase 3 studies are presented below.

6.3.1 Edema-Related Adverse Events

Edema-Related Adverse Events in the Short-term Phase

Table 6.3.1 shows edema-related adverse events during the CV168006ST phase. The incidence of edema was dose related above the muraglitazar 5 mg dose threshold, and the incidences in the muraglitazar 0.5 mg, 1.5 mg, 5 mg and the pioglitazone 15 mg group were similar. The highest rate of all edema-related adverse events was seen in the muraglitazar 20 mg group.

Table 6.3.1: Number (Percent) of Subjects Who Reported Edema-Related Adverse Events During the Short-term Phase by Treatment Group (CV168006)

SYSTEM ORGAN CLASS (%) PREFERRED TERM (%)	BMS 0.5MG N = 236	BMS 1.5MG N = 259	BMS 5MG N = 245	BMS 10MG N = 249	BMS 20MG N = 237	PIO 15MG N = 251
TOTAL SUBJECTS WITH Edema-related AE	25 (10.6)	25 (9.7)	21 (8.6)	62 (24.9)	95 (40.1)	36 (14.3)

SUBJECTS MAY HAVE HAD THE ABOVE EVENTS AT MULTIPLE TIMES
Edema-related AES are based upon a pre-defined list of preferred terms.

6.3.2 Congestive Heart Failure

Seven cases of heart failure were reported during the ST phase of Study CV168006 (Table 6.3.2). Five of these events (2.0%) occurred in subjects taking 10 mg of muraglitazar and 2 events (0.8%) occurred in subjects taking 20 mg of muraglitazar. Although discontinuation of study drug was advised in the protocol, heart failure events in 4 of the 7 subjects were managed with diuretics and/or other therapies and these 4 subjects continued in the study without interruption of muraglitazar dosing. There were no cases of heart failure reported for subjects who received muraglitazar ≤ 5 mg or pioglitazone 15 mg.

Table 6.3.2: Subjects who Experienced Heart Failure in the Short-Term Phase (CV168006)

Identification Number	Dose (mg)	Onset Day	Relationship to Study Drug	Intensity	Subject status for this AE	Resolution for this Heart Failure Event
CV168006-252-3	Muraglitazar 10	50	Unrelated	Mild	Continued	Resolved on Day 58[a]
CV168006-114-5	Muraglitazar 10	62	Possible	Moderate	Continued	Discontinued on Day 70[b]; Resolved by Day 86
CV168006-280-3	Muraglitazar 10	88	Possible	Severe	Discontinued	Resolved 26 days after discontinuation
CV168006-91-1	Muraglitazar 10	117	Probable	Moderate	Discontinued	Resolved 22 days after discontinuation
CV168006-226-9	Muraglitazar 10	150	Probable	Moderate	Continued	Resolved 8 days later[c]
CV168006-36-9	Muraglitazar 20	24	Possible	Mild	Discontinued	Resolved 5 days after discontinuation
CV168006-164-6	Muraglitazar 20	92	Unlikely	Severe	Continued	Resolved 3 days later[d]

[a] Subject CV168006-252-3 experienced another heart failure event (moderate) on Day 140 of the ST phase which resolved after 4 days; and experienced another heart failure event (severe) on Day 475 of the LT phase which led to discontinuation

[b] Subject CV168006-114-5 was discontinued on Day 70 for worsening generalized edema

[c] Subject CV168006-226-9 was discontinued on Day 576 of the LT phase for bladder cancer

[d] Subject CV168006-164-6 experienced another heart failure event (severe) on Day 190 of the LT phase; study medication was discontinued 30 days after the onset of this severe heart failure event which was ongoing but improving (weight decreased 5 lb and no shortness of breath) at the time of the subject's final study visit.

6.3.3 Change from Baseline in Body Weight

During the ST phase of study CV168006, baseline mean weights ranged from 88.35 kg to 90.97 kg across all dose groups (Table 6.3.3). At Week 24, there was a mean decrease from baseline in body weight for the muraglitazar 0.5 mg and 1.5 mg groups. There was a dose-related mean increase from baseline in body weight for the muraglitazar 5 mg, 10 mg and 20 mg groups ranging from 1.61 kg to 4.85 kg. The pioglitazone 15 mg group had a mean increase from baseline in body weight of 0.19 kg.

Table 6.3.3: Change from Baseline in Body Weight at Week 24 LOCF - Each dose level of Muraglitazar relative to Pioglitazone 15 mg (CV168006ST)

Measure: Body Weight Unit: kg	Mura 0.5MG N=236	Mura 1.5MG N=259	Mura 5MG N=245	Mura 10MG N=249	Mura 20MG N=237	PIO 15MG N=251
Summary Statistics						
n	231	253	235	245	236	245
Baseline Mean (SD)	88.35 (17.01)	88.87 (17.27)	88.87 (16.93)	88.95 (18.04)	90.97 (16.87)	90.61 (16.99)
Week 24 LOCF Mean (SD)	87.22 (16.85)	88.65 (17.57)	90.48 (18.04)	92.14 (18.65)	95.84 (17.91)	90.82 (17.77)
Mean Change from Bsl. (SD)	-1.13 (3.41)	-0.22 (3.09)	1.60 (3.66)	3.19 (4.24)	4.87 (4.63)	0.20 (3.35)
Adjusted Change from Baseline						
Mean (SE)	-1.12 (0.25)	-0.21 (0.24)	1.61 (0.25)	3.20 (0.24)	4.85 (0.24)	0.19 (0.24)
95% two-sided CI	[-1.61, -0.64]	[-0.68, 0.25]	[1.13, 2.09]	[2.73, 3.67]	[4.37, 5.33]	[-0.28, 0.66]
Difference in Adjusted Change from Baseline vs PIO 15MG						
Mean (SE) (1)	-1.31 (0.34)	-0.40 (0.34)	1.42 (0.34)	3.01 (0.34)	4.66 (0.34)	
95% two-sided CI	[-1.98, -0.63]	[-1.06, 0.26]	[0.75, 2.09]	[2.34, 3.67]	[3.99, 5.33]	

6.4 Dose Selection Considerations and Conclusion

The robust efficacy and safety results from this large dose-ranging study, CV168006, that evaluated approximately 245 subjects for each treatment arm helped to define the doses that were evaluated further in Phase 3 monotherapy and combination therapy clinical trials. At the upper end, the muraglitazar 5 mg dose was selected as the top dose because it provided strong glycemic and lipid efficacy without demonstrating the higher overall incidence of adverse events for edema, weight gain and heart failure that was apparent for the muraglitazar 10 and 20 mg dose groups. In fact, muraglitazar 5 mg in this monotherapy dose-ranging trial was indistinguishable from the lower dose groups (0.5 mg and 1.5 mg) and the pioglitazone 15 mg group in relative incidence rates of edema and the absence of any heart failure events during the first 24 weeks of treatment. Muraglitazar 5 mg was also discernibly better in glycemic control, especially in added lipid efficacy, compared with muraglitazar 1.5 mg or pioglitazone 15 mg.

At the bottom end, the muraglitazar 1.5 mg dose in Study CV168006 was not selected for Phase 3 studies because it resulted in improvement of A1C less than 0.7% (the historic regulatory standard for clinically significant efficacy) and fewer than 50% of the subjects reaching the ADA target of A1C < 7%. Rather, a muraglitazar 2.5 mg dose was selected as the lowest dose for the Phase 3 program for multiple reasons. The similar incidence of edema at doses less than or equal to 5 mg suggested that the 2.5 mg dose would give greater efficacy than 1.5 mg with a similar incidence of edema. In addition, muraglitazar 2.5 mg was projected by dose-response modeling to be capable of improving A1C by at least 0.7% and providing glycemic control in at least 50% of the subjects. This added response was felt to be beneficial and needed not only in the monotherapy setting but also in the combination therapy trials that were planned as part of the muraglitazar Phase 3 clinical program. Finally, a choice of 2.5 mg also provides a simple dose multiple for the 5 mg dose.

In conclusion, the doses of muraglitazar selected for Phase 3 studies were 2.5 mg and 5 mg QD. These doses were based on robust 24-week efficacy and safety data obtained from a large set of type 2 diabetes subjects requiring monotherapy who were treated either with various doses of muraglitazar (1226 subjects) or with pioglitazone (251 subjects) in the Phase 2 dose-ranging study CV168006. Subjects who completed the ST

phase of CV168006 were eligible to enter the LT extension phase of this trial. The LT data, which evaluate the durability of efficacy and the assurance of safety over time, are discussed in Section 7.7 and Section 8. Of note, future development plans include studying the muraglitazar 10 mg dose as a titration dose for subjects who need additional glycemic control.

7 PHASE 2 AND 3 CLINICAL STUDIES - EFFICACY

7.1 Overview

The muraglitazar Phase 2/3 clinical efficacy program includes data for 4640 treated subjects (4320 treated subjects with type 2 diabetes and 320 non-diabetic subjects with mixed dyslipidemia). Of these 4320 subjects with type 2 diabetes, 3226 were treated with muraglitazar, 823 were treated with pioglitazone and 591 were treated with placebo. The clinical program included 5 studies that were conducted in subjects with type 2 diabetes - 2 monotherapy studies (CV168006 and CV168018) and 3 combination therapy studies (CV168021 with glyburide, and CV168022 and CV168025 with metformin). The monotherapy studies included subjects who were to be recently untreated with oral diabetes medications while the combination therapy studies included subjects whose diabetes was inadequately controlled with sulfonylurea or metformin alone. These studies included male and female subjects between ages 18 and 70 years with baseline A1C values ranging between 7% - 10%. In addition, subjects with screening A1C values ranging between 10%-12% were included in the open-label (OL) treatment cohort in CV168018. The primary efficacy endpoint was the change from baseline in A1C at Week 24. ST data (24 weeks) are available for all studies, and LT data are available for CV168006 (total treatment of 104 weeks) and CV 168025 (total treatment of 50 weeks).

In addition to the studies in subjects with type 2 diabetes, Study CV168008 was conducted in a non-diabetic population with mixed dyslipidemia. ST data (6 weeks) and LT data (total treatment of 106 weeks) are included in the NDA submission. Synopses for this study are attached to this document as Attachment 3.1A (ST phase) and Attachment 3.1B (LT phase) and are not further discussed in the body of this document.

7.2 Study Descriptions - Phase 2/3 Studies

Data from 5 clinical studies in type 2 diabetic subjects form the basis of the NDA submission. These studies are referred to throughout this document by study number or study identifier as indicated in Table 7.2A

Table 7.2A: Study Identifiers

Study Number[a]	Comparator	Study Description
CV168006	pioglitazone	Phase 2 monotherapy dose-ranging study
CV168018	placebo	Phase 3 monotherapy
CV168021	placebo	Phase 3 combination with sulfonylurea
CV168022	placebo	Phase 3 combination with metformin
CV168025	pioglitazone	Phase 3 combination with metformin

[a] An "ST" or "LT" designation after the study number indicates either the ST phase (generally 24 weeks) or the LT phase (generally ≥ 1 year depending on the study)

Table 7.2B presents a summary of the doses, duration and number of subjects treated for these 5 clinical studies.

Table 7.2B: Overview of Phase 2 and 3 Clinical Studies in Type 2 Diabetes

Study	Muraglitazar Dose (mg)	Total Treated (N = 4640)	Muraglitazar (N = 3226)	Comparator (N = 1414)	Duration of Therapy (weeks)	
					ST	ST + LT
CV168006[a] (monotherapy)	0.5, 1.5, 5, 10, or 20	1477	1226	251 (pioglitazone 15 mg)	24	104
CV168018 (monotherapy)	2.5 or 5	340	225	115 (placebo)	24	NA
	5 (OL cohort)[b]	109	109	NA	24	NA
CV168021 (combination w/ glyburide)	2.5 or 5	583	384	199 (placebo)	24	102[c]
CV168022 (combination w/ metformin)	2.5 or 5	652	438	214 (placebo)	24	102[c]

Table 7.2B: Overview of Phase 2 and 3 Clinical Studies in Type 2 Diabetes

CV168025 (combination w/ metformin)	5	1159	587	572 (pioglitazone 30 mg)	24	50
Totals for subjects with type 2 diabetes		4320	2969	1351		

[a] Dose titration was permitted once during the ST period and as often as needed during the LT double-blind extension.

[b] Subjects with a screening A1C >10% and ≤ 12% who met all other inclusion/exclusion criteria were eligible for direct enrollment into the 5 mg muraglitazar OL cohort

[c] Study is still ongoing.

Type 2 Diabetes: Phase 2/3 Monotherapy Studies

Study CV168006 was a dose-ranging study that included a ST phase with the possibility of dose titration (i.e. rescue) and a LT phase. The rescue component allowed subjects that did not meet prespecified glycemic parameters during the ST treatment phase to be titrated once to a higher dose of the drug to which they were randomized. Subjects who completed the ST double-blind phase, including those that required rescue treatment, could enter a LT, double-blind treatment phase. In the LT phase, if the prespecified glycemic parameters were not met, the subject could continue to be titrated to the next dose, up to and including the highest dose allowed in the protocol (20 mg for muraglitazar and 45 mg for pioglitazone). The protocol was later amended to down titrate subjects who were on muraglitazar 20 mg to muraglitazar 10 mg. Data from the LT phase (up to 104 weeks including the 24-week ST phase) are provided in this document. The ST and LT phases (periods B & C) of the study are completed and a LT extension phase (up to 4 years total) of the study is ongoing.

Study CV168018 was a Phase 3, randomized, 3-arm, parallel group, double-blind, placebo-controlled, multicenter trial of the antihyperglycemic activity of 2 doses (2.5 mg and 5 mg) of muraglitazar in drug-naïve subjects with type 2 diabetes who had inadequate glycemic control, defined as a screening A1C ≥ 7.0% and ≤ 10.0%. Subjects with a screening A1C > 10.0% and ≤ 12.0% who met all other inclusion/exclusion

criteria were eligible for direct enrollment into the OL treatment cohort and were treated with 5 mg muraglitazar.

Type 2 Diabetes: Phase 3 Combination Therapy Studies

Study CV168021 was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, 3-arm study that evaluated the effect of muraglitazar 2.5 or 5 mg compared with placebo on a background of glyburide in subjects with type 2 diabetes who were not adequately controlled with sulfonylurea therapy alone. Subjects who completed the 24-week ST, double-blind phase could enter a LT, double-blind treatment phase (for a total of 102 weeks). The ST phase is completed and the LT phase is ongoing.

Study CV168022 is a Phase 3, randomized, double-blind, placebo-controlled, 3-arm study that evaluated the effect of muraglitazar 2.5 or 5 mg compared with placebo on a background of metformin in subjects with type 2 diabetes who were not adequately controlled with metformin alone. Subjects who completed the 24-week ST, double-blind phase could enter a LT, double-blind treatment phase (for a total of 102 weeks). The ST phase is completed and the LT phase is ongoing.

Study CV168025 is a Phase 3, randomized, double-blind, active-controlled study that evaluated the effect of muraglitazar 5 mg vs pioglitazone 30 mg on a background of metformin in subjects with type 2 diabetes who were not adequately controlled with metformin alone. Subjects who completed the 24-week ST, double-blind phase could enter a LT, double-blind treatment phase (for a total of 50 weeks). Both the ST and LT phases are complete.

Key Inclusion Criteria for these 5 clinical studies included:

- A1C ≥ 7% and ≤ 10%
- Men and women, 18-70 years
- Body Mass Index (BMI) ≤ 41 kg/m2
- serum TG ≤ 600 mg/dL
- for Phase 3 protocols only fasting C-peptide > 1.5 ng/mL

Key Exclusion Criteria for these 5 clinical studies included:

- NYHA Class III and IV (Class II also excluded in Phase 2 protocol only)

- Symptomatic type 2 diabetes defined as marked polyuria and polydipsia with > 10% weight loss during the last three months
- History of myocardial infarction (MI), angioplasty or bypass graft(s), valvular disease or repair, unstable angina pectoris, transient ischemic attack or cerebrovascular accidents within six months prior to entry into the study.
- Aspartate transaminae (AST) or ALT >2.5 x ULN and/or serum total bilirubin >2 x ULN
- Current treatment with fibrates
- Serum creatinine > 1.8 mg/dL (or > 1.5 mg/dL for male and > 1.4 mg/dL for female subjects in studies using metformin)

Medications:

- No fibrate use during the first 12 weeks (24 weeks in Phase 2 protocol) of the ST phase; after that period of time, if clinically indicated, a fibrate could be initiated
- No initiation of a statin during the first 12 weeks of ST phase; Subjects already on a statin could not alter the dose during this same time period; after this time period a statin could be initiated or titrated
- No statin and fibrate combination at any time during the study
- No niacin, ezetimibe, bile-acid binding agents, or probucol

Key Endpoints for these 5 clinical studies included:

- Change in A1C from baseline to Week 24
- Change in FPG from baseline to Week 24
- Percent change in lipid levels (HDL-C, TG, non-HDL-C, and apoB) from baseline to Week 12

7.3 Statistical Considerations in Type 2 Diabetes Studies

For efficacy analyses, data from the different studies are presented individually to show consistency of results across studies. Data were not pooled across studies due to different study designs, treatment groups and study populations.

In each study, the analysis of the primary endpoint, i.e. change from baseline in A1C to Week 24 was based on an ANCOVA model with treatment group as the effect, and with the baseline value as a covariate. Although preliminary assessments suggested non-

normality, the confidence intervals for the treatment means are believed to be robust due to the large sample size. However to be conservative, a non-parametric rank-based ANCOVA model was used to report p-values rather than a parametric test. The primary comparisons were between each of the muraglitazar treatment arms and the control arm. A sequential testing procedure was used to preserve an overall significance level of 0.05 and each comparison was performed at a two-sided $\alpha = 0.05$ level.

Other glycemic and lipid parameters were analyzed using a similar ANCOVA model. Unless otherwise stated all analyses on the efficacy parameters used the LOCF methodology. For simplicity, the word LOCF was omitted in the following sections. In addition, results of mean changes (or mean percent changes) from baseline reported in the following sections refer to adjusted mean (percent) changes from baseline.

All studies were designed as superiority studies, except study CV168025 which was designed as a non-inferiority study. For this study, muraglitazar 5 mg plus metformin was to be considered not inferior to pioglitazone 30 mg plus metformin if the upper limit of the two-sided 95% CI of the difference in change in A1C from baseline to Week 24 LOCF between the 2 treatment groups was 0.25% or less. Furthermore, if non-inferiority was demonstrated then the superiority of muraglitazar 5 mg plus metformin against pioglitazone 30 mg plus metformin was to be tested.

Subjects included in the efficacy analyses are those randomized (or enrolled in the open-label cohort of CV168018), who received at least 1 dose of ST study medication, and who have a baseline value and at least 1 post-baseline measurement for the parameter. In addition, for analyses of A1C only subjects who received treatment for at least 6 weeks were included, to allow enough time to see a change in A1C. Subjects who received treatment for at least 8 days were included in the analyses of FPG.

Statistical testing strategy for secondary endpoints

In order to protect the overall type I error at a 0.05 level, in the phase 3 placebo-controlled studies a sequential testing procedure was used to perform the comparisons of selected secondary endpoints following the prespecified order listed below, if and only if the superiority of both muraglitazar doses were demonstrated at the 0.05 level. In this

sequential testing procedure, once a non-significant p-value was obtained, no further p-values were reported for the remaining comparisons in the sequence.

1) Comparison between muraglitazar 5 mg and placebo for FPG,
2) Comparison between muraglitazar 5 mg and placebo for fasting TG,
3) Comparison between muraglitazar 2.5 mg and placebo for FPG,
4) Comparison between muraglitazar 2.5 mg and placebo for fasting TG.

Similarly, for study CV168025, if non-inferiority of muraglitazar 5 mg was demonstrated then a sequential testing procedure was used to perform the comparisons between muraglitazar 5 mg and pioglitazone 30 mg for the secondary endpoints listed below:

1) TG,
2) TG in subgroup of subjects with baseline TG ≥ 150 mg/dL,
3) HDL-C,
4) ApoB,
5) Non-HDL-C.

In the phase 3 placebo-controlled studies, p-values were generated post-hoc for the comparison between each of the muraglitazar arms and placebo for percent change in HDL-C from baseline to Week 11/12.

Long-term efficacy

The LT efficacy of monotherapy (up to muraglitazar 5 mg) was examined in this document using the data collected for up to 104 weeks of the ST combined with LT phase of study CV168006. Data for subjects who were randomized to muraglitazar 1.5 mg, 5 mg, or pioglitazone 15 mg and who started the LT phase on the same treatment and dose are included in Section 7.7.2 of this document. For the two muraglitazar arms in the LT phase, only efficacy measurements prior to any titration and prior to the receipt of adjunctive antihyperglycemic medication were included. For the pioglitazone arm in the LT phase, all efficacy measurements including those obtained after titration to pioglitazone 45 mg were used, providing they were collected prior to the receipt of adjunctive antihyperglycemic medications.

7.4 Phase 2/3 Study Results - Glycemic Parameters

7.4.1 Monotherapy Studies - CV168006 and CV168018

Study CV168006

Results for the ST phase of this Phase 2 monotherapy dose-ranging study are presented in Section 6 of this document. For comparison, results for selected muraglitazar doses in this study are repeated in Table 7.4.1A next to results from monotherapy study CV168018.

Study CV168018

Treatment with muraglitazar 2.5 mg and 5 mg doses produced statistically significant ($p < 0.0001$) and clinically meaningful reductions from baseline in A1C levels at Week 24 compared to placebo (Table 7.4.1A). Subjects taking muraglitazar 2.5 mg, 5 mg or placebo had a mean change from baseline in A1C of -1.05%, -1.23%, or -0.32%, respectively.

In addition, dose-dependent decreases in other glycemic and glycemic-related parameters were observed at Week 24 (Table 7.4.1A):

- The mean changes from baseline in FPG were significantly greater ($p < 0.0001$) in the muraglitazar 2.5 mg (-25.61 mg/dL) and 5 mg groups (-32.76 mg/dL) compared to the placebo group (1.07 mg/dL); baseline mean FPG values were lower in the placebo group than in the muraglitazar groups.
- The proportion of subjects with a final A1C < 7% was greater in the muraglitazar 2.5 mg and 5 mg groups (58.1% and 71.8%, respectively) than in the placebo group (29.7%).
- The mean change from baseline in fasting insulin levels was greater in the muraglitazar 2.5 and 5 mg groups (-2.85 µU/mL and -3.10 µU/mL, respectively) than in the placebo group (0.94 µU/mL).
- The mean change from baseline in fasting C-peptide values was greater in the muraglitazar 2.5 and 5 mg groups (-0.51 ng/mL and -0.78 ng/mL, respectively) than in the placebo group (-0.27 ng/mL).
- The mean percent change from baseline in free fatty acid (FFA) values was -19.33% for muraglitazar 2.5 mg and -30.58% for muraglitazar 5 mg relative to -9.40% for placebo.

Study CV168018 - Muraglitazar 5 mg Open-Label (OL) Cohort

The muraglitazar 5 mg OL cohort (109 subjects) had a higher mean baseline A1C value, 10.68%, that made achieving good glycemic control more difficult. However, muraglitazar 5 mg resulted in an unadjusted mean change at Week 24 for A1C of -2.62%, with a mean change from baseline for FPG of −68.4 mg/dL. By Week 24, 38.8% of subjects had achieved a goal of A1C < 7% (Table 7.4.1A and Table 7.4.1B). Sixty-two of the subjects completed the study and had data available at Week 24. For these subjects the mean change from baseline in A1C was -3.49%.

Table 7.4.1A: Results for Glycemic Parameters at Week 24 (LOCF), Monotherapy

	CV168006			CV168018			
Parameter	**Mur 1.5 N=259**	**Mur 5 N=245**	**Pio 15 N=251**	**Mur 2.5 N=111**	**Mur 5 N=114**	**Pla N=115**	**Mur 5 OL N=109**
A1C (%)	**n=235**	**n=227**	**n=230**	**n=105**	**n=110**	**n=111**	**n=98**
Baseline Mean (SD)	8.15 (1.05)	8.23 (1.01)	8.31 (1.10)	8.02 (1.02)	7.89 (0.99)	7.99 (1.05)	10.68 (0.83)
Adjusted Mean Change from Baseline (SE)	-0.57 (0.07)	-1.18 (0.07)	-0.57 (0.07)	-1.05 (0.09)	-1.23 (0.09)	-0.32 (0.09)	-2.62 (0.18) unadjusted
Difference from Control Group (95% CI)				-0.73 (-0.97, -0.48)	-0.91 (-1.15, -0.67)		NA
Rank p-value	NA	NA	NA	< 0.0001	< 0.0001	NA	NA
Final A1C < 7 % (%)	95 (40.4%)	133 (58.6%)	98 (42.6%)	61 (58.1%)	79 (71.8%)	33 (29.7%)	38 (38.8%)
FPG (mg/dL)	**n=250**	**n=232**	**n=242**	**n=111**	**n=112**	**n=114**	**n=106**
Baseline Mean (SD)	180.39 (54.18)	182.44 (51.07)	192.71 (51.45)	168.48 (53.84)	169.79 (53.87)	162.17 (40.57)	235.2 (55.5)
Adjusted Mean Change from Baseline (SE)	-20.33 (2.37)	-40.40 (2.46)	-22.49 (2.42)	-25.61 (3.26)	-32.76 (3.25)	1.07 (3.22)	-68.4 (4.77) unadjusted
Difference from Control Group (95% CI)				-26.69 (-35.70, -17.67)	-33.84 (-42.84, -24.83)		NA
Rank p-value				< 0.0001	< 0.0001		

Table 7.4.1A: Results for Glycemic Parameters at Week 24 (LOCF), Monotherapy

	CV168006			CV168018			
Parameter	**Mur 1.5 N=259**	**Mur 5 N=245**	**Pio 15 N=251**	**Mur 2.5 N=111**	**Mur 5 N=114**	**Pla N=115**	**Mur 5 OL N=109**
Fasting Insulin (μU/mL)	**n=178**	**n=181**	**n=165**	**n=99**	**n=104**	**n=99**	**n=89**
Baseline Mean (SD)	15.26 (10.44)	14.20 (10.74)	15.33 (9.07)	18.45 (19.04)	13.56 (9.37)	15.65 (8.98)	11.54 (7.23)
Adjusted Mean Change from Baseline (SE)	-1.00 (0.39)	-3.38 (0.39)	-0.81 (0.51)	-2.85 (0.78)	-3.10 (0.76)	0.94 (0.77)	-0.42 (0.69) **unadjusted**
Difference from Control Group (95% CI)				-3.79 (-5.96, -1.63)	-4.04 (-6.17, -1.90)		NA
Fasting C-peptide (ng/mL)[a]	**n = 182**	**n = 179**	**n = 166**	**n = 100**	**n = 104**	**n = 99**	**n = 89**
Baseline Mean (SD)	3.47 (1.53)	3.30 (1.39)	3.43 (1.52)	3.33 (1.60)	3.20 (1.30)	3.32 (1.25)	2.90 (1.15)
Adjusted Mean Change from Baseline (SE)[a]	-0.37 (0.07)	-0.90 (0.07)	-0.64 (0.07)	-0.51 (0.08)	-0.78 (0.08)	-0.27 (0.08)	-0.51 (0.10) **unadjusted**
Difference from Control Group (95% CI)				-0.24 (-0.46, -0.02)	-0.52 (-0.74, -0.30)		NA
Free Fatty Acid (mEq/L)	**n = 191**	**n = 196**	**n = 175**	**n = 104**	**n = 108**	**n = 104**	**n = 89**
Baseline Mean (SD)	0.51 (0.21)	0.53 (0.21)	0.52 (0.19)	0.68 (0.24)	0.70 (0.23)	0.68 (0.24)	0.72 (0.03)*
Adjusted Mean % Change from Baseline (SE)	-19.26 (2.66)	-20.94 (2.57)	-13.66 (2.70)	-19.33 (2.85)	-30.58 (2.41)	-9.40 (3.20)	-32.14 (2.85)**
95% two-sided CI				(-19.29, -1.76)	(-30.50, -15.52)		

[a] Fasting only for CV168018.

* geometric mean

** unadjusted geometric mean

Table 7.4.1B: Number (Percent) of Subjects Achieving Glycemic Response (A1C) at Week 24 (LOCF) during the Double-blind Phase and in the Open-Label Cohort (CV168018)

	Mur 2.5 N=111	Mur 5 N=114	PLA N=115	Mur 5 OL N=109
Number of Subjects with Available Data:	105	110	111	98
A1C < 6.5%	33 (31.4%)	64 (58.2%)	15 (13.5%)	27 (27.6%)
A1C < 7%	61 (58.1%)	79 (71.8%)	33 (29.7%)	38 (38.8%)

N = Number of Randomized or Open-Label Cohort Subjects

7.4.2 Combination Therapy Study with Sulfonylurea - CV168021

Muraglitazar showed clinical benefit as therapy for subjects with type 2 diabetes in combination with sulfonylurea. Primary efficacy endpoint results at Week 24 (LOCF) showed the mean change from baseline in A1C was significantly greater in the muraglitazar 2.5 and 5 mg groups (-1.00% and -1.21%, respectively) compared with the placebo group (0.16%). Reduction from baseline in FPG, fasting insulin, fasting C-peptide and FFA were observed with muraglitazar at Week 24 and are presented in Table 7.4.2, along with the percent to A1C goal.

At Week 24 (Table 7.4.2.):

- The mean change from baseline in FPG values was statistically significantly ($p < 0.0001$) greater in the muraglitazar 2.5 mg and 5 mg groups (-26.74 mg/dL and -35.96 mg/dL, respectively) compared with the placebo group (11.59 mg/dL).
- The proportions of subjects with a final A1C < 7% were greater in the muraglitazar 2.5 and 5 mg groups (52.3% and 58.7%, respectively) than in the placebo group (13.3%).
- The mean change from baseline in fasting insulin values was greater in the muraglitazar 2.5 mg and 5 mg groups (-1.66 µU/mL and -3.45 µU/mL, respectively) than in the placebo group (1.17 µU/mL).
- The mean change from baseline in fasting C-peptide levels was greater in the muraglitazar 2.5 mg and 5 mg groups (-0.39 and -0.65 ng/mL, respectively) than in the placebo group (-0.09 ng/mL).

- The mean percent change from baseline in free fatty acid (FFA) values was -16.95% for muraglitazar 2.5 mg and -20.93% for muraglitazar 5 mg groups relative to -2.57% for placebo the placebo group.

Table 7.4.2: Changes from Baseline in Glycemic Parameters at Week 24 (LOCF), Combination with Sulfonylurea

Parameter	CV168021		
	Mur 2.5+Gly (N=191)	**Mur 5+Gly (N=193)**	**Pla+Gly (N=199)**
A1C (%)	**n=176**	**n=189**	**n=195**
Baseline Mean (SD)	7.95 (1.09)	8.17 (1.08)	8.23 (0.97)
Adjusted Mean Change from Baseline (SE)	-1.00 (0.07)	-1.21 (0.07)	0.16 (0.07)
Difference from Control Group (95% CI)	-1.15 (-1.35, -0.96)	-1.37 (-1.55, -1.18)	NA
Rank p-value	< 0.0001	< 0.0001	NA
Final A1C < 7 % (%)	92 (52.3)	111 (58.7)	26 (13.3)
FPG (mg/dL)	**n=182**	**n=191**	**n=196**
Baseline Mean (SD)	161.58 (43.21)	169.27 (51.37)	167.05 (49.13)
Adjusted Mean Change from Baseline (SE)	-26.74 (2.77)	-35.96 (2.71)	11.59 (2.67)
Difference from Control Group (95% CI)	-38.34 (-45.90, -30.77)	-47.55 (-55.02, -40.09)	NA
Rank P value	<0.0001	<0.0001	NA
Fasting Insulin (μU/mL)	**n=170**	**n=184**	**n=184**
Baseline Mean (SD)	16.19 (10.60)	14.51 (8.87)	16.30 (10.30)
Adjusted Mean Change from Baseline (SE)	-1.66 (0.56)	-3.45 (0.54)	1.17 (0.54)
Difference from Control Group (95% CI)	-2.82 (-4.34, -1.31)	-4.62 (-6.11, -3.13)	NA
Fasting C-peptide (ng/mL)	**n=172**	**n=188**	**n=189**
Baseline Mean (SD)	3.34 (1.22)	3.31 (1.24)	3.39 (1.27)
Adjusted Mean Change from Baseline (SE)	-0.39 (0.07)	-0.65 (0.07)	-0.09 (0.06)
Difference from Control Group (95% CI)	-0.30 (-0.48, -0.11)	-0.56 (-0.74, -0.38)	NA
Free Fatty Acids (FFA) (mEq/L)	**n = 175**	**n = 187**	**n = 190**
Baseline Mean (SD)	0.64 (0.24)	0.66 (0.24)	0.63 (0.23)
Adjusted Mean % Change from Baseline (SE)	-16.95 (2.35)	-20.93 (2.17)	-2.57 (2.64)
Difference from Control Group (95% CI)	-14.75 (-21.07, -7.93)	-18.84 (-24.77, -12.45)	NA

7.4.3 Combination Therapy Study with Metformin - CV168022 and CV168025

The effects of muraglitazar in combination with metformin were evaluated in two studies. Study CV168022 compared muraglitazar 2.5 mg and 5 mg vs placebo when added to metformin and study CV168025 compared muraglitazar 5 mg + metformin vs. pioglitazone 30 mg + metformin. Study CV168025 provides important comparator information about a standard of care, pioglitazone, and the proposed top dose of muraglitazar, 5 mg. This study was designed as a non-inferiority study in which it was predetermined that an A1C difference of 0.25% would be considered clinically significant. If non-inferiority was achieved, then testing for superiority was to be done.

Study CV 168022

Treatment with muraglitazar 2.5 mg and 5 mg on a background of metformin produced statistically significant ($p < 0.0001$) and clinically meaningful reductions from baseline in A1C levels at Week 24 compared to placebo (Table 7.4.3). Subjects taking muraglitazar 2.5 mg, 5 mg or placebo had a mean change from baseline in A1C of -0.91%, -1.16%, or -0.05%, respectively.

Study CV168025

Muraglitazar 5 mg on a background of metformin resulted in an A1C difference of -0.29% from baseline at Week 24 which was statistically significant and clinically meaningful compared to pioglitazone 30 mg on a background of metformin (Table 7.4.3). Subjects receiving muraglitazar 5 mg + metformin had a mean change from baseline in A1C of -1.14% vs. -0.85 % for pioglitazone 30 mg + metformin ($p < 0.0001$).

Reductions from baseline in FPG, fasting insulin, fasting C-peptide and FFA were observed with muraglitazar as compared to pioglitazone at Week 24 and are presented in Table 7.4.3, along with the percent to A1C goal.

Table 7.4.3: Changes from Baseline in Glycemic Parameters at Week 24 (LOCF), Combination with Metformin

Parameter	CV168022			CV168025	
	Mur 2.5+Met (N=233)	Mur 5+Met (N=205)	Pla+Met (N=214)	Mur 5+Met (N=587)	Pio 30+Met (N=572)
A1C (%)	**n=222**	**n=198**	**n=197**	**n=569**	**n=550**
Baseline Mean (SD)	7.99 (0.99)	8.00 (0.99)	7.97 (1.01)	8.12 (0.96)	8.13 (1.00)
Adjusted Mean Change from Baseline (SE)	-0.91 (0.06)	-1.16 (0.07)	-0.05 (0.07)	-1.14 (0.04)	-0.85 (0.04)
Difference from Control Group (95% CI)	-0.86 (-1.04, -0.67)	-1.11 (-1.30, -0.92)	NA	-0.29 (-0.39, -0.19)	NA
Rank p-value	< 0.0001	< 0.0001	NA	<0.0001	NA
Final A1C < 7 % (%)	119 (53.6)	127 (64.1)	53 (26.9)	340 (59.8)	245 (44.5)
FPG (mg/dL)	**n=228**	**n=200**	**n=211**	**n=577**	**n=567**
Baseline Mean (SD)	169.44 (42.66)	167.15 (45.37)	170.91 (50.67)	179.08 (50.00)	177.69 (49.40)
Adjusted Mean Change from Baseline (SE)	-25.56 (2.40)	-35.16 (2.57)	-2.12 (2.50)	-43.52 (1.21)	-32.69 (1.22)
Difference from Control Group (95% CI)	-23.45 (-30.25, -16.64)	-33.04 (-40.08, -26.01)	NA	-10.84 (-14.21, -7.46)	NA

Table 7.4.3: Changes from Baseline in Glycemic Parameters at Week 24 (LOCF), Combination with Metformin

Parameter	CV168022			CV168025	
	Mur 2.5+Met (N=233)	Mur 5+Met (N=205)	Pla+Met (N=214)	Mur 5+Met (N=587)	Pio 30+Met (N=572)
Fasting Insulin (μU/mL)	**n=213**	**n=190**	**n=190**	**n=555**	**n=536**
Baseline Mean (SD)	12.78 (9.37)	12.64 (8.59)	14.62 (14.53)	15.02 (9.71)	15.16 (12.51)
Adjusted Mean Change from Baseline (SE)	-1.89 (0.43)	-2.68 (0.46)	-0.13 (0.46)	-4.95 (0.21)	-3.58 (0.22)
Difference from Control Group (95% CI)	-1.75 (-2.99, -0.51)	-2.54 (-3.82, -1.27)	NA	-1.37 (-1.97, -0.77)	NA
Fasting C-peptide (ng/mL)	**n=217**	**n=192**	**n=196**	**n=560**	**n=544**
Baseline Mean (SD)	2.93 (1.26)	2.91 (1.20)	3.16 (1.41)	3.11 (1.20)	3.08 (1.23)
Adjusted Mean Change from Baseline (SE)	-0.42 (0.07)	-0.68 (0.07)	-0.11 (0.07)	-0.62 (0.03)	-0.45 (0.03)
Difference from Control Group (95% CI)	-0.32 (-0.52, -0.12)	-0.58 (-0.78, -0.37)	NA	-0.17 (-0.26, -0.08)	NA
Free Fatty Acid (mEq/L)	**n = 217**	**n = 192**	**n = 196**	**n = 560**	**n = 540**
Baseline Mean (SD)	0.69 (0.25)	0.70 (0.22)	0.67 (0.27)	0.66 (0.22)	0.66 (0.24)
Adjusted Mean % Change from Baseline (SE)	-17.67 (1.93)	-28.03 (1.80)	-6.68 (2.31)	-24.12 (1.25)	-14.88 (1.42)
Difference from Control Group (95% CI)	-11.78 (-17.49, -5.68)	-22.88 (-28.03, -17.37)	NA	-10.85 (-14.86, -6.66)	NA

7.5 Phase 2 and 3 Study Results - Lipid Parameters

The effects of muraglitazar on lipid parameters were examined using similar methodologies in both the monotherapy and combination therapy studies. Subjects were required to maintain a stable dose of HMG-CoA reductase inhibitor (i.e. statin) prior to entering the study and during the first 12 weeks. However, after Week 12 subjects were allowed to add (e.g. a statin or fibrate but not both in combination) or adjust lipid lowering medication. Therefore, the analysis of lipid parameters was done at the Week 12 timepoint. A subanalysis of subjects receiving lipid lowering therapy (i.e. statin) did not reveal significant differences in lipid parameters relative to subjects not receiving concomitant lipid lowering therapy. Overall, approximately 22% of subjects in the Phase 2/3 studies were treated with statins.

In study CV168008, which investigated 3 doses of muraglitazar (5 mg, 10 mg, and 20 mg) vs placebo in a non-diabetic dyslipidemic population there were dose dependent and statistically significant reductions from baseline to week 6 in TG levels as well as increases in HDL-C concentrations. In addition, there was another treatment arm which combined muraglitazar 20 mg plus pravastatin 40 mg. The results from this arm showed even greater reductions in TG levels and increases in HDL-C (See Attachment 3.1A for a summary of Study CV168008).

7.5.1 Monotherapy Studies - CV168006 and CV168018

Muraglitazar treatment resulted in statistically significant reductions from baseline in TG levels and increases in HDL-C levels at week 12 compared to control. Since the testing strategy for secondary endpoints did not include apoB and non-HDL-C, no p values for the comparison vs control were generated. However, there were clinically meaningful decreases in these parameters. Reductions in apoB reflect increases in LDL particle size which may be an even more beneficial effect on cardiovascular risk. Also, there were minimal changes in LDL-C and TC. Overall, there was a greater impact on the lipid endpoints with the muraglitazar 5 mg dose (Table 7.5.1). Results at Week 24 indicate the effects observed at Week 12 were maintained.

Table 7.5.1: Changes from Baseline in Lipids at Week 12 LOCF, Monotherapy Studies

	CV168006			CV168018		
Lipid Parameter	MUR 1.5 N=259	MUR 5 N=245	PIO 15 N=251	MUR 2.5 N=111	MUR 5 N=114	PLA N=115
TG (mg/dL)	n = 251	n = 234	n = 243	n = 111	n = 112	n = 114
Baseline Mean (SD)	188.73 (136.17)	186.30 (116.00)	189.14 (114.15)	192.83 (93.98)	194.07 (99.38)	186.85 (110.45)
Adj.Mean %Change from Bsl	-6.64	-21.23	-9.25	-17.93	-27.44	-1.72
95% CI	[-10.74, -2.35]	[-24.81,-17.49]	[-13.29, -5.01]	[-22.74,-12.83]	[-31.67,-22.95]	[-7.41, 4.32]
rank p value				0.0001	<0.0001	
HDL-C (mg/dL)	n = 252	n = 234	n = 244	n = 111	n = 112	n = 114
Baseline Mean (SD)	43.44 (10.14)	42.37 (9.64)	43.14 (10.27)	43.78 (9.04)	42.05 (10.18)	45.31 (10.87)
Adj.Mean %Change from Bsl	7.85	17.36	10.01	9.64	16.10	2.43
95% CI	[5.90, 9.82]	[15.17, 19.60]	[8.00, 12.06]	[7.17, 12.18]	[13.47, 18.78]	[0.14, 4.78]
rank p value				<0.0001	<0.0001	
Apo B (mg/dL)	n = 194	n = 192	n = 178	n = 111	n = 112	n = 114
Baseline Mean (SD)	109.40 (49.02)	106.22 (26.90)	108.75 (25.07)	102.99 (24.06)	102.11 (25.33)	104.28 (24.88)
Adj.Mean %Change from Bsl	-5.02	-9.69	-4.73	-7.40	-12.13	0.13
95% CI	[-7.51, -2.46]	[-12.07, -7.24]	[-7.34, -2.05]	[-10.12, -4.60]	[-14.70, -9.49]	[-2.77, 3.11]
LDL-C (mg/dL)	n = 251	n = 234	n = 242	n = 111	n = 112	n = 114
Baseline Mean (SD)	122.76 (31.94)	121.66 (33.52)	127.13 (37.33)	129.62 (36.48)	124.17 (31.17)	131.51 (37.13)
Adj.Mean %Change from Bsl	-1.81	2.83	3.18	-0.74	-1.41	1.16
95% CI	[-4.27, 0.72]	[0.16, 5.58]	[0.54, 5.88]	[-3.83, 2.46]	[-4.48, 1.75]	[-1.95, 4.38]
Total-C (mg/dL)	n = 252	n = 234	n = 244	n = 111	n = 112	n = 114
Baseline Mean (SD)	202.37 (39.44)	200.81 (38.87)	207.73 (39.05)	199.26 (41.05)	193.51 (36.46)	202.18 (40.73)
Adj.Mean %Change from Bsl	-0.03	0.96	1.78	0.35	-0.10	1.55
95% CI	[-1.69, 1.67]	[-0.79, 2.74]	[0.05, 3.54]	[-1.67, 2.42]	[-2.11, 1.95]	[-0.47, 3.61]

Dataset: Randomized Subjects
N=Number of Randomized Subjects, n=Number of Randomized Subjects with available data
Summary statistics only presented for a treatment group if at least 20 subjects in this treatment group have available data
ANCOVA model: log(post)-log(pre)=log(pre) treatment
ANCOVA model for the estimates in CV168006 included muraglitazar 0.5, 1.5, 5, 10, 20 mg, and pioglitazone 15 mg groups

Table 7.5.1: Changes from Baseline in Lipids at Week 12 LOCF, Monotherapy

	CV168006			CV168018		
Lipid Parameter	MUR 1.5 N=259	MUR 5 N=245	PIO 15 N=251	MUR 2.5 N=111	MUR 5 N=114	PLA N=115
Non-HDL-C (mg/dL)	n = 252	n = 234	n = 244	n = 111	n = 112	n = 114
Baseline Mean (SD)	158.92 (38.92)	158.44 (38.17)	164.59 (38.78)	155.53 (41.77)	151.46 (36.54)	156.87 (37.74)
Adj.Mean %Change from Bsl	-2.28	-3.71	-0.66	-2.96	-5.27	0.91
95% CI	[-4.45, -0.06]	[-5.93, -1.44]	[-2.91, 1.63]	[-5.59, -0.27]	[-7.82, -2.64]	[-1.78, 3.68]

Dataset: Randomized Subjects
N=Number of Randomized Subjects, n=Number of Randomized Subjects with available data
Summary statistics only presented for a treatment group if at least 20 subjects in this treatment group have available data
ANCOVA model: log(post)-log(pre)=log(pre) treatment
ANCOVA model for the estimates in CV168006 included muraglitazar 0.5, 1.5, 5, 10, 20 mg, and pioglitazone 15 mg groups

7.5.2 Combination Therapy Studies with Sulfonylurea - CV168021

At Week 12 muraglitazar produced clinically meaningful effects on TG, HDL-C, apoB, and non-HDL-C. As previously stated (Section 7.5.1) for apoB and non-HDL-C no p-values were generated for the comparison between muraglitazar and placebo. However, there were clinically meaningful reductions in apoB and non-HDL-C and minimal changes in LDL-C and total cholesterol (Total-C) (Table 7.5.2).

Table 7.5.2: Changes from Baseline in Lipids at Week 12 (LOCF), Combination Therapy with Sulfonylurea

	CV168021		
Lipid Parameter	MUR 2.5+GLY N=191	MUR 5+GLY N=193	PLA+GLY N=199
TG (mg/dL)	n = 183	n = 192	n = 197
Baseline Mean (SD)	196.67 (116.38)	203.62 (110.23)	192.95 (110.62)
Adj.Mean %Change from Bsl	-13.87	-26.12	3.18
95% CI	[-17.73, -9.84]	[-29.35,-22.74]	[-1.28, 7.84]
rank p value	<0.0001	<0.0001	
HDL-C (mg/dL)	n = 183	n = 192	n = 197
Baseline Mean (SD)	44.02 (10.03)	43.78 (9.99)	44.32 (10.13)
Adj.Mean %Change from Bsl	7.37	13.72	-0.24
95% CI	[5.65, 9.12]	[11.94, 15.52]	[-1.79, 1.32]
rank p value	<0.0001	<0.0001	
Apo B (mg/dL)	n = 183	n = 192	n = 197
Baseline Mean (SD)	103.78 (23.45)	107.08 (25.96)	103.46 (23.18)
Adj.Mean %Change from Bsl	-5.46	-11.49	-0.28
95% CI	[-7.66, -3.22]	[-13.49, -9.44]	[-2.51, 2.00]
LDL-C (mg/dL)	n = 183	n = 192	n = 197
Baseline Mean (SD)	118.91 (33.96)	121.26 (35.21)	117.96 (32.30)
Adj.Mean %Change from Bsl	3.59	2.38	2.94
95% CI	[0.84, 6.42]	[-0.28, 5.11]	[0.30, 5.65]
Total-C (mg/dL)	n = 183	n = 192	n = 197
Baseline Mean (SD)	200.48 (38.78)	204.83 (40.22)	199.93 (36.42)
Adj.Mean %Change from Bsl	1.12	-1.13	1.65
95% CI	[-0.71, 2.98]	[-2.87, 0.65]	[-0.12, 3.45]
Non-HDL-C (mg/dL)	n = 183	n = 192	n = 197
Baseline Mean (SD)	156.46 (38.28)	161.05 (39.76)	155.61 (36.11)
Adj.Mean %Change from Bsl	-0.94	-5.51	2.23
95% CI	[-3.26, 1.44]	[-7.67, -3.29]	[-0.08, 4.60]

Dataset: Randomized Subjects
N=Number of Randomized Subjects, n=Number of Randomized Subjects with available data
Summary statistics only presented for a treatment group if at least 20 subjects in this treatment group have available data
ANCOVA model: log(post)-log(pre)=log(pre) treatment

7.5.3 Combination Therapy Studies with Metformin - CV168022 & CV168025

At Week 12, reductions from baseline in TG and apoB, and increases in HDL-C were greater for subjects treated with muraglitazar 2.5 and 5 mg compared with placebo (Study CV168022) or for subjects treated with muraglitazar 5 mg compared with the highest dose (30 mg at the time) of pioglitazone approved at the time for use in combination therapy (Study CV168025) (Table 7.5.3). In study CV168022 these changes were statistically significant for TG and HDL-C. As the testing strategy did not include apoB and non HDL-C, no p-values were generated for the comparisons between muraglitazar and placebo. However, there were clinically meaningful reductions in apoB. In Study CV168025, there were statistically significant changes from baseline for TG, HDL-C, and apoB vs the comparator, pioglitazone 30 mg. Approximately 24% of subjects in these two combination therapy trials were treated with statins. Overall, there was no effect of muraglitazar on LDL-C or total cholesterol. Results at Week 24 indicate the effects observed at Week 12 were maintained.

Table 7.5.3: Summary of Changes in Lipids at Week 12 LOCF, Combination Therapy with Metformin

	CV168022			CV168025	
Lipid Parameter	MUR 2.5+MET N=233	MUR 5+MET N=205	PLA+MET N=214	MUR 5+MET N=587	PIO 30+MET N=572
TG (mg/dL)	n = 228	n = 201	n = 212	n = 571	n = 555
Baseline Mean (SD)	197.79 (116.07)	208.02 (121.48)	197.01 (177.78)	205.50 (125.09)	202.75 (128.44)
Adj.Mean %Change from Bsl	-13.88	-29.20	3.22	-28.43	-14.44
95% CI	[-17.38,-10.23]	[-32.27,-26.00]	[-1.13, 7.77]	[-30.16,-26.66]	[-16.53,-12.29]
rank p value	<0.0001	<0.0001		<0.0001	
HDL-C (mg/dL)	n = 228	n = 201	n = 212	n = 571	n = 555
Baseline Mean (SD)	45.00 (9.21)	45.79 (10.91)	46.17 (9.95)	46.29 (11.12)	45.92 (11.14)
Adj.Mean %Change from Bsl	8.00	14.14	0.95	19.16	13.61
95% CI	[6.43, 9.59]	[12.37, 15.94]	[-0.58, 2.49]	[18.03, 20.31]	[12.52, 14.72]
rank p value	<0.0001	<0.0001		<0.0001	
Apo B (mg/dL)	n = 228	n = 200	n = 212	n = 571	n = 555
Baseline Mean (SD)	99.64 (25.55)	100.01 (22.24)	98.90 (36.01)	100.85 (24.64)	100.61 (26.78)
Adj.Mean %Change from Bsl	-4.98	-11.91	0.95	-11.75	-5.96
95% CI	[-6.85, -3.06]	[-13.77,-10.01]	[-1.11, 3.07]	[-12.96,-10.52]	[-7.27, -4.64]
rank p value				<0.0001	
LDL-C (mg/dL)	n = 228	n = 201	n = 212	n = 571	n = 555
Baseline Mean (SD)	106.77 (33.15)	106.25 (31.75)	105.81 (31.36)	113.41 (34.95)	112.63 (33.38)
Adj.Mean %Change from Bsl	8.61	5.20	4.91	2.80	3.53
95% CI	[6.03, 11.25]	[2.54, 7.93]	[2.33, 7.56]	[1.24, 4.39]	[1.94, 5.16]
Total-C (mg/dL)	n = 228	n = 201	n = 212	n = 571	n = 555
Baseline Mean (SD)	189.95 (37.58)	191.36 (37.10)	189.22 (38.48)	198.56 (40.95)	196.63 (39.45)
Adj.Mean %Change from Bsl	3.41	0.30	3.53	0.39	2.54
95% CI	[1.86, 4.98]	[-1.30, 1.93]	[1.92, 5.17]	[-0.55, 1.34]	[1.57, 3.52]

Dataset: Randomized Subjects
N=Number of Randomized Subjects, n=Number of Randomized Subjects with available data
Summary statistics only presented for a treatment group if at least 20 subjects in this treatment group have available data
ANCOVA model: log(post)-log(pre)=log(pre) treatment

Table 7.5.3: Summary of Changes in Lipids at Week 12 LOCF, Combination Therapy with Metformin

	CV168022			CV168025	
Lipid Parameter	MUR 2.5+MET N=233	MUR 5+MET N=205	PLA+MET N=214	MUR 5+MET N=587	PIO 30+MET N=572
Non-HDL-C (mg/dL)	n = 228	n = 201	n = 212	n = 571	n = 555
Baseline Mean (SD)	144.95 (37.45)	145.56 (35.94)	143.05 (38.78)	152.26 (39.67)	150.71 (39.03)
Adj.Mean %Change from Bsl	1.81	-4.56	4.37	-5.88	-1.22
95% CI	[-0.21, 3.86]	[-6.57, -2.50]	[2.23, 6.56]	[-7.09, -4.65]	[-2.51, 0.09]
rank p value				<0.0001	

Dataset: Randomized Subjects
N=Number of Randomized Subjects, n=Number of Randomized Subjects with available data
Summary statistics only presented for a treatment group if at least 20 subjects in this treatment group have available data
ANCOVA model: log(post)-log(pre)=log(pre) treatment

7.6 Additional Efficacy Parameters

7.6.1 Effects on Postprandial Glucose and Insulin levels

The postprandial effects of muraglitazar were studied in drug-naïve subjects in the monotherapy study (CV168018) since this population provided the best opportunity to examine muraglitazar's effects without possible confounding by a concomitant anti-hyperglycemic agent. A 3-hour Boost® meal challenge was done at randomization and at study completion with analysis of glucose and insulin using comparisons of AUC values (Table 7.6.1A and Table 7.6.1B). Both glucose and insulin AUC values decreased following treatment with muraglitazar 2.5 mg and 5 mg. These findings suggest that muraglitazar not only lowers postprandial glucose but does so with less insulin (ie, improves insulin resistance and/or beta cell function).

Table 7.6.1A: Change from Baseline in 3 Hour Postprandial Glucose AUC at Week 24 (LOCF) During the Double-Blind Phase: Each Dose of Muraglitazar vs Placebo (CV168018)

Measure: AUC_P Unit: mg*min/dL	MUR 2.5 N=111	MUR 5 N=114	PLA N=115
Summary Statistics			
n	89	94	91
Baseline Mean (SD)	35971 (10047)	36081 (10298)	35098 (9739.3)
Week 24 (LOCF) Mean (SD)	28879 (6749.9)	26296 (7712.6)	35820 (10584)
Mean Change from Bsl. (SD)	-7092 (9163.8)	-9785 (7425.3)	721.98 (8673.5)
Adjusted Change from Baseline			
Mean (SE)	-6967 (725.17)	-9606 (705.70)	415.38 (717.54)
95% two-sided CI	[-8395, -5540]	[-10996, -8217]	[-997.3, 1828.1]
Difference in Adjusted Change from Baseline vs PLA			
Mean (SE) (1)	-7383 (1020.4)	-10022 (1006.8)	
95% two-sided CI	[-9392, -5374]	[-12004, -8040]	

Data set: Randomized Subjects
Notes: ANCOVA model: post-pre=pre treatment.
(1) Estimate = Adjusted Mean Change - Adjusted Mean Change for PLA

Table 7.6.1B: Change from Baseline in 3 Hour Postprandial AUC for Insulin at Week 24 (LOCF) During the Double-Blind Phase: Each Dose of Muraglitazar vs Placebo (CV168018)

Measure: AUC_I Unit: uU*min/mL	MUR 2.5 N=111	MUR 5 N=114	PLA N=115
Summary Statistics			
n	85	88	85
Baseline Mean (SD)	6370.9 (4245.3)	5642.7 (3505.7)	6739.8 (3999.9)
Week 24 (LOCF) Mean (SD)	6232.9 (3859.8)	5026.4 (2805.1)	6767.3 (3851.7)
Mean Change from Bsl. (SD)	-138.0 (3175.1)	-616.4 (2293.8)	27.53 (3027.1)
Adjusted Change from Baseline			
Mean (SE)	-92.46 (269.57)	-832.2 (265.96)	205.45 (270.23)
95% two-sided CI	[-623.3, 438.41]	[-1356, -308.4]	[-326.7, 737.64]
Difference in Adjusted Change from Baseline vs PLA			
Mean (SE) (1)	-297.9 (381.44)	-1038 (380.39)	
95% two-sided CI	[-1049, 453.27]	[-1787, -288.5]	

Data set: Randomized Subjects
Notes: ANCOVA model: post-pre=pre treatment.
(1) Estimate = Adjusted Mean Change - Adjusted Mean Change for PLA

7.6.2 Homeostasis Model Assessment

HOMA is a calculated value derived from fasting glucose and insulin that is used to estimate insulin resistance (HOMA-IR) or beta cell function (HOMA-%B). Higher HOMA-IR values are associated with increased insulin resistance, whereas higher HOMA-%B values are associated with increased/improved beta-cell function. HOMA-IR and HOMA-%B values were examined in the monotherapy study (CV168018) since drug-naïve monotherapy subjects provided the best opportunity to examine the effects of muraglitazar without possible confounding effects of other anti-glycemic agents.

The median baseline HOMA-IR value ranged from 4.3 to 5.6 across the study groups (including the OL cohort). At Week 24 there was a 9.4% median increase from baseline in HOMA-IR value for the placebo group. In contrast, there was a decrease in median percent change from baseline in HOMA-IR value of 23.9% in the muraglitazar 2.5 mg

group, 35.6% in the muraglitazar 5 mg group, and 37.9% in the muraglitazar 5 mg open-label cohort in Study CV168018 (Table 7.6.2A). These changes indicate that muraglitazar improved insulin sensitivity (i.e. decreased insulin resistance). At Week 24 the median percent change from baseline was 5.5 % in the HOMA-%B value for the placebo group and was 27.7%, 32.3% and 90.7% for the muraglitazar 2.5 mg, 5mg and 5 mg OL groups, respectively (Table 7.6.2B). This data suggests that muraglitazar increased or improved beta cell function.

Table 7.6.2A: Percent Change from Baseline in HOMA-IR at Week 24 (LOCF) during the Double-Blind Phase and in the Open-Label Cohort (CV168018)

		IR-HOMA								
		Baseline			Week 24			Percent Change From Baseline		
Treatment	N	Q1	Median	Q3	Q1	Median	Q3	Q1	Median	Q3
MUR 2.5	99	3.29	4.7	7.08	2.65	3.8	5.34	-46.94	-23.9	5.74
MUR 5	103	2.75	4.3	7.03	1.86	3.0	4.93	-52.19	-35.6	0.13
PLA	98	3.34	5.2	8.36	3.55	5.6	8.45	-26.18	9.4	51.18
MUR 5 OL	89	3.24	5.6	8.73	1.97	3.5	5.32	-57.40	-37.9	-3.29

Table 7.6.2B: Percent Change from Baseline in BHOMA at Week 24 (LOCF)during the Double-Blind Phase and in the Open-Label Cohort, CV168018

		BHOMA								
		Baseline			Week 24			Percent Change From Baseline		
Treatment	N	Q1	Median	Q3	Q1	Median	Q3	Q1	Median	Q3
MUR 2.5	99	34.26	55.0	88.28	41.62	67.7	98.50	-12.50	27.7	55.40
MUR 5	103	24.69	47.2	77.40	37.96	67.7	107.63	4.13	32.3	85.78
PLA	98	31.52	53.1	89.80	35.81	55.7	83.32	-16.99	5.5	38.49
MUR 5 OL	89	13.09	22.8	36.03	25.47	42.6	78.30	32.28	90.7	159.25

7.6.3 Other Metabolic Markers

Multiple metabolic markers have been implicated in the pathogenesis of cardiovascular disease. Several of the more compelling and clinically meaningful markers such as hs-CRP, and thrombotic markers, PAI-1 and fibrinogen had consistent and reproducible decreases across the Phase 2 and 3 studies. Data for these metabolic markers is presented only for study CV168018 since this placebo controlled, drug-naïve, monotherapy population provided the best opportunity to examine the effects of muraglitazar on these metabolic markers vs control.

7.6.3.1 High Sensitivity C-reactive Protein (hs-CRP)

Table 7.6.3.1 presents the reduction from baseline in hs-CRP at Week 24 (LOCF) during the double-blind phase of Study CV168018. Mean percent changes from baseline at Week 24 were -20.46% and -33.71% for muraglitazar 2.5 mg and 5 mg, respectively, with a -8.36% change for placebo. Reductions in hs-CRP reflect the anti-inflammatory activity of muraglitazar in the macrophages, which may play an important part in cardiovascular risk reduction.

Table 7.6.3.1: Percent Change from Baseline in hs-CRP at Week 24 (LOCF) during Double-Blind Phase (CV168018)

Measure: HS-CRP Unit: mg/L	MUR 2.5 N=111	MUR 5 N=114	PLA N=115
Week: 24			
Summary Statistics			
n	101	106	101
Baseline Mean (SD)	3.42 (4.04)	4.37 (6.23)	3.29 (2.91)
Onstudy LOCF Mean (SD)	2.58 (2.26)	2.85 (4.26)	3.64 (5.36)
Adjusted % Change from Baseline			
Mean (SE)	-20.46 (5.72)	-33.71 (4.65)	-8.36 (6.58)
95% two-sided CI	[-30.95, -8.37]	[-42.27, -23.89]	[-20.43, 5.54]
Difference in Adjusted % Change from Baseline vs PLA			
Mean (SE) (1,2)	-13.20 (8.81)	-27.67 (7.27)	
95% two-sided CI	[-28.92, 6.00]	[-40.64, -11.86]	

Data set: Randomized Subjects
Notes: ANCOVA model: log(post)-log(pre)=log(pre) treatment.
(1) Estimate = (((Adjusted Mean % Change+100)/(Adjusted Mean % Change for PLA+100))-1)*100
(2) SE = 100*Adjusted Change from Baseline Geometric mean*SE in logarithms.

7.6.3.2 Plasminogen Activator Inhibitor-1 (PAI-1)

Table 7.6.3.2 presents the percent reduction from baseline in PAI-1 at Week 24 (LOCF) during the double-blind phase of Study CV168018. Mean percent changes from baseline at Week 24 were -16.32% and -23.87% for muraglitazar 2.5 mg and 5 mg, respectively, with a 4.39% increase for placebo.

Table 7.6.3.2: Percent Change from Baseline in PAI-1 at Week 24 (LOCF) during Double-Blind Phase (CV168018)

Measure: PAI-1 Unit: ng/mL	MUR 2.5 N=111	MUR 5 N=114	PLA N=115
Summary Statistics			
n	101	104	98
Baseline Mean (SD)	48.17 (28.02)	47.71 (27.80)	47.21 (20.95)
Week 24 LOCF Mean (SD)	44.43 (46.94)	36.85 (21.97)	49.49 (25.24)
Adjusted % Change from Baseline			
Mean (SE)	-16.32 (3.93)	-23.87 (3.52)	4.39 (4.97)
95% two-sided CI	[-23.70, -8.22]	[-30.50, -16.62]	[-4.95, 14.65]
Difference in Adjusted % Change from Baseline vs PLA			
Mean (SE) (1,2)	-19.84 (5.36)	-27.07 (4.84)	
95% two-sided CI	[-29.73, -8.56]	[-36.01, -16.89]	

Data set: Randomized Subjects
Notes: ANCOVA model: log(post)-log(pre)=log(pre) treatment.
(1) Estimate = (((Adjusted Mean % Change+100)/(Adjusted Mean % Change for PLA+100))-1)*100
(2) SE = 100*Adjusted Change from Baseline Geometric mean*SE in logarithms.

7.6.3.3 Fibrinogen

Table 7.6.3.3 presents the results of muraglitazar on the mean reduction from baseline in fibrinogen at Week 24 during the double-blind phase of Study CV168018. Mean percent changes from baseline at Week 24 were -2.95% and -6.87% for muraglitazar 2.5 mg and 5 mg, respectively, with a 0.81% increase for placebo.

Table 7.6.3.3: Percent Change from Baseline in Fibrinogen at Week 24 (LOCF) during Double-Blind Phase (CV168018)

Measure: Fibrinogen Unit: mg/dL	MUR 2.5 N=111	MUR 5 N=114	PLA N=115
Summary Statistics			
n	100	103	99
Baseline Mean (SD)	348.24 (80.00)	371.58 (101.61)	344.67 (63.39)
Week 24 LOCF Mean (SD)	338.24 (69.59)	337.71 (85.42)	350.90 (68.12)
Adjusted % Change from Baseline			
Mean (SE)	-2.95 (1.81)	-6.87 (1.71)	0.81 (1.89)
95% two-sided CI	[-6.45, 0.67]	[-10.18, -3.43]	[-2.84, 4.59]
Difference in Adjusted % Change from Baseline vs PLA			
Mean (SE) (1,2)	-3.73 (2.54)	-7.61 (2.43)	
95% two-sided CI	[-8.60, 1.40]	[-12.27, -2.70]	

Notes: ANCOVA model: log(post)-log(pre)=log(pre) treatment.
(1) Estimate = (((Adjusted Mean % Change+100)/(Adjusted Mean % Change for PLA+100))-1)*100
(2) SE = 100*Adjusted Change from Baseline Geometric mean*SE in logarithms.

7.6.3.4 Urinary Albumin-to-Creatinine Ratio

Muraglitazar treatment also resulted in significant improvements in urinary albumin/creatinine ratios with up to 30% median decrease in urinary albumin/creatinine ratios (Table 7.6.3.4). This early proteinuria biomarker is widely monitored for diabetes mellitus and a reduction has been suggested to provide some protection from LT renal and cardiovascular morbidity in subjects with type 2 diabetes.[20]

Table 7.6.3.4: Median Change From Baseline in Albumin-to-Creatinine Ratio at Week 24 (Phase 3 ST Studies)

	Placebo	Muraglitazar 2.5 mg	Muraglitazar 5 mg	Pioglitazone 30 mg
Monotherapy				
Baseline	3.0	2.0	3.0	--
% Mean Change	0.0	-19.7	-25.0	--
Combination w/Glyburide				
Baseline	11.0	9.0	10.0	--
% Mean Change	0.0	-8.8	-8.4	--
Combination w/Metformin				
Baseline	7.0	8.0	10.0	--
% Mean Change	0.0	-20.0	-25.0	--
TZD Comparator				
Baseline	--	--	10.0	8.0
% Mean Change	--	--	-33.3	-21.2

7.7 Long-term Efficacy - Durability of Control

The LT efficacy of muraglitazar is presented from two clinical studies. The TZD comparator study (CV168025) was designed to evaluate the ability of muraglitazar to maintain glycemic control over 1 year. The Phase 2 dose-ranging study (CV168006) permitted evaluation of muraglitazar LT treatment over two years.

7.7.1 TZD Comparator Study (CV168025)

The mean change from baseline in A1C at Week 50 demonstrated sustained and greater reduction in A1C for muraglitazar 5 mg plus metformin (-1.13%) compared to pioglitazone 30 mg plus metformin (-0.74%) (Table 7.7.1). The difference in mean change from baseline between the two treatment groups at Week 50 was -0.39%, which was statistically significant ($p < 0.0001$).

Table 7.7.1: Change from Baseline in A1C at Week 50 LOCF (CV168025)

Measure: A1C Unit: %	MUR 5+MET N=587	PIO 30+MET N=572
Summary Statistics		
n	569	550
Baseline Mean (SD)	8.12 (0.96)	8.13 (1.00)
Week 50 LOCF Mean (SD)	6.99 (1.07)	7.39 (1.17)
Mean Change from Bsl. (SD)	-1.12 (0.95)	-0.74 (1.08)
Adjusted Change from Baseline		
Mean (SE)	-1.13 (0.04)	-0.74 (0.04)
95% two-sided CI	[-1.20, -1.05]	[-0.81, -0.66]
Difference in Adjusted Change from Baseline vs PIO 30+MET		
Mean (SE) (1)	-0.39 (0.06)	
Rank p-value	<.0001	
95% two-sided CI	[-0.50, -0.28]	

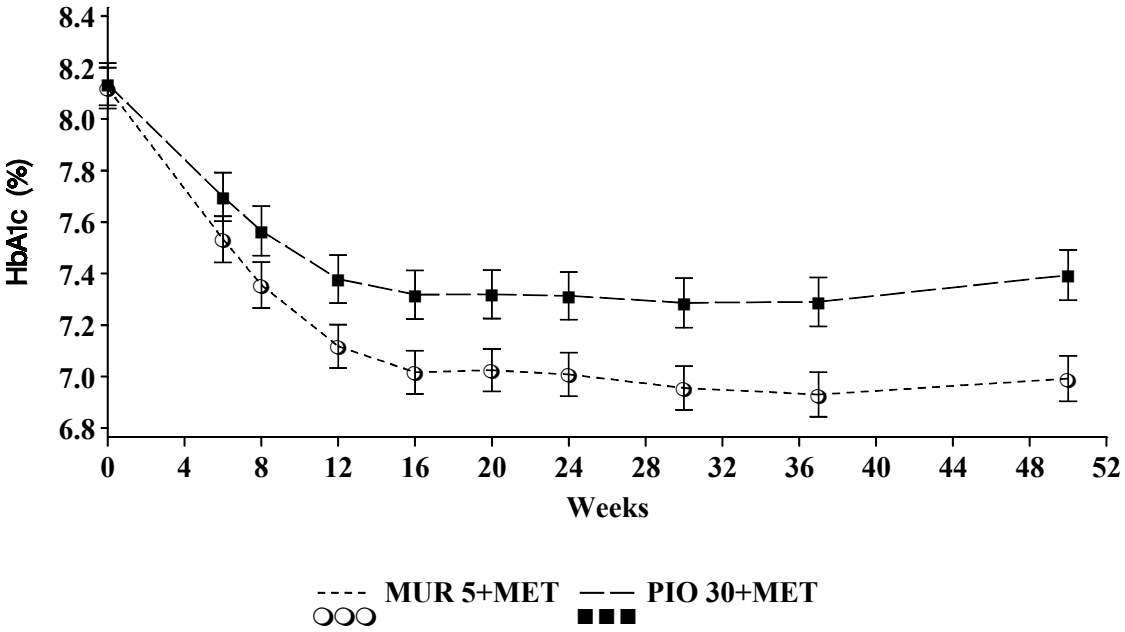
Dataset: Randomized Subjects
Notes: ANCOVA model: post-pre=pre treatment.
(1) Estimate = Adjusted Mean Change - Adjusted Mean Change for PIO 30+MET

7.7.1.1 Change in A1C Over Time

The A1C values were assessed at pre-specified time points starting from baseline to Week 50. The muraglitazar 5 mg plus metformin group showed larger decreases from baseline in A1C at each specified time of assessment during the study relative to the pioglitazone 30 mg plus metformin group (Figure 7.7.1.1). While both treatment groups had very similar baseline mean A1C values (8.1) an initial separation between the two treatment groups was apparent by Week 8. The difference between the two treatment groups was maintained through Week 50, with a mean final A1C value of 6.99% for the

muraglitazar 5 mg plus metformin arm compared to 7.39% for pioglitazone 30 mg plus metformin.

Figure 7.7.1.1: Plot of Mean and 95% CI for A1C at Each Time Point LOCF During the 50-Week Period (CV168025)



At Baseline: N = 586 for Mura 5 mg; N = 572 for Pio 30 mg

At Week 50: N = 569 for Mura 5 mg; N = 550 for Pio 30 mg
Dataset: Randomized Subjects:

7.7.2 Dose-ranging Study CV168006

The dose-ranging study provides clinically important data about the LT efficacy over 2 years for subjects who stayed on the same muraglitazar or pioglitazone dose through the 24 weeks of the ST phase.

The durability of glycemic control for the muraglitazar 1.5 mg and 5 mg doses and for the pioglitazone 15 mg dose is presented using the data collected for up to 104 weeks. This combines ST and LT phase data. This analysis focuses on subjects who were randomized to muraglitazar 1.5 mg or 5 mg, or pioglitazone 15 mg and who started the

LT phase on the same treatment and dose. For the two muraglitazar arms in the LT phase, only efficacy measurements prior to any titration and prior to the receipt of adjunctive antihyperglycemic medication were included. On the other hand, for the pioglitazone arm in the LT phase, all efficacy measurements including those obtained after titration to pioglitazone 45 mg were used, provided they were collected prior to the receipt of adjunctive antihyperglycemic medications. The pioglitazone 45 mg titration data were included to allow for a more clinically meaningful comparator arm.

7.7.2.1 Mean Change from Baseline in A1C at Week 104

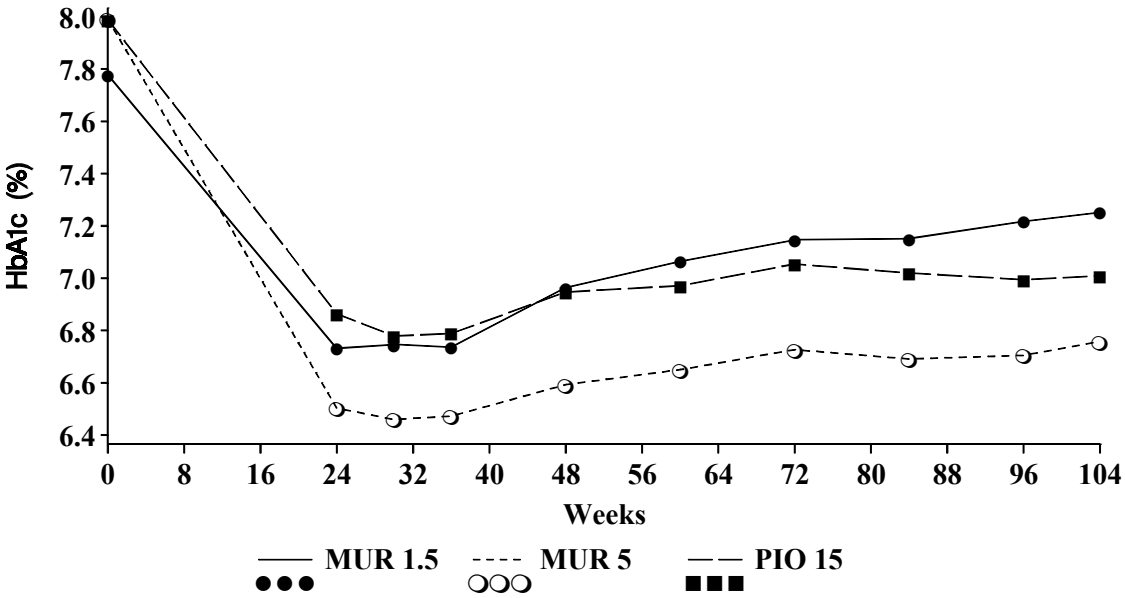
There were 2 types of LT analyses performed on the change from baseline in A1C: 1) using the LOCF approach, and 2) using available data at each time point (observed data).

Mean Change from Baseline in A1C (LOCF)

In the LOCF analysis, the subgroup of subjects treated with muraglitazar 5 mg achieved a mean A1C < 7% at Week 24 and maintained it over 104 weeks (Figure 7.7.2.1A). This subgroup was initially randomized to muraglitazar 5 mg as part of a larger cohort (n = 245). Of this cohort, 54 subjects discontinued from the study in the ST phase, including 4 subjects discontinuing due to lack of glycemic control. A total of 48 subjects randomized to muraglitazar 5 mg were rescued to muraglitazar 10 mg. The subjects that remained on muraglitazar 5 mg during the ST phase were allowed to continue on the same treatment in the LT phase. This subgroup of subjects on muraglitazar 5 mg (n = 157) had a mean baseline A1C of 7.99%, and had a mean decrease from baseline in A1C of 1.23% to achieve a final mean A1C of 6.76% at Week 104.

Subjects who were randomized to muraglitazar 1.5 mg and remained on this dose at the start of the LT phase (n = 132) had a mean baseline A1C of 7.78%, and had a mean decrease from baseline A1C of 0.53% to achieve a final mean A1C of 7.25% at Week 104. By Week 104, there were 43 subjects who were titrated from muraglitazar 1.5 mg to muraglitazar 5 mg or higher. The group of subjects who were randomized to and started the LT phase on pioglitazone 15 mg (n = 146) had a mean baseline A1C of 7.99%, and had a mean decrease from baseline in A1C of 0.98% to achieve a final mean A1C of 7.01% at Week 104.

Figure 7.7.2.1A: Plot of Mean A1C levels (LOCF) Over Time by Treatment in the Long-term Phase of CV168006



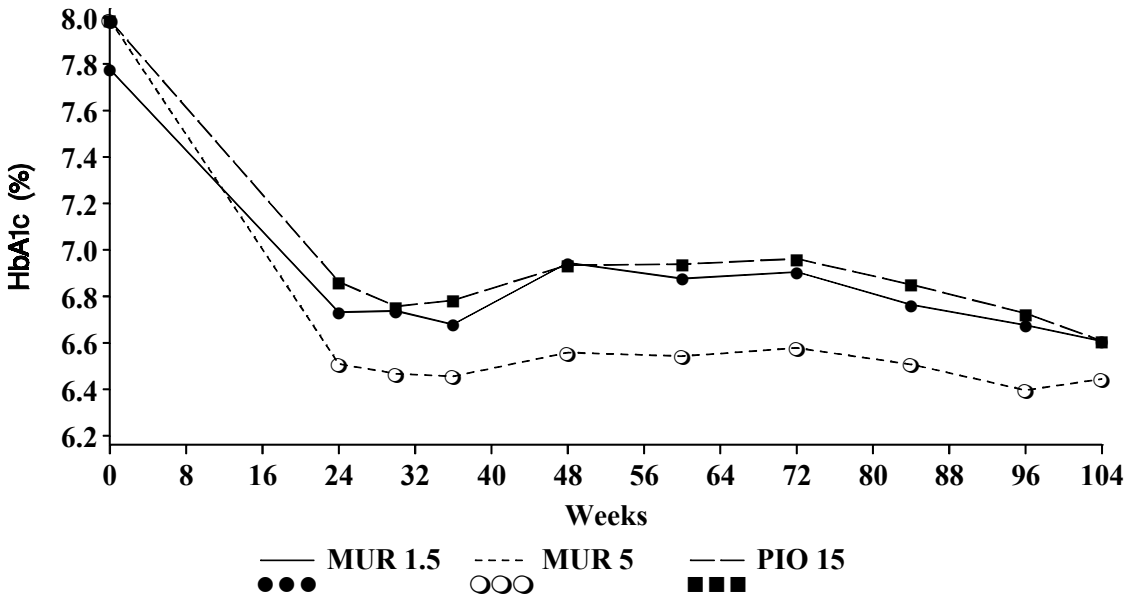
At Baseline and Week 104: Mur 1.5 mg N = 132; Mur 5 mg N = 157; Pio 15 mg N = 146
Dataset: Randomized Subjects

Mean Change From Baseline in A1C (Observed Data)

Using available data at each time point (observed data) the analysis of A1C over the 104 week period also demonstrated reductions with all treatment arms (Figure 7.7.2.1B).

At Week 104, there were 88 subjects who remained on muraglitazar 5 mg (with a mean baseline A1C of 7.92%) and had a mean decrease from baseline A1C of 1.48% to achieve a final mean A1C of 6.44%.

Figure 7.7.2.1B: Plot of Mean A1C levels (Available Data) Over Time by Treatment in the Long-Term Phase of CV168006



	Baseline (n)	Week 24 (n)	Week 48 (n)	Week 72 (n)	Week 104 (n)
Mur 1.5	132	132	120	96	61
Mur 5	157	153	136	116	88
Pio 15	146	141	133	113	80

Dataset: Randomized Subjects

At Week 104, there were 61 subjects who remained on muraglitazar 1.5 mg (with a mean baseline A1C of 7.49%) and had a mean decrease from baseline A1C of 7.69% and a mean decrease from baseline of 0.88% to achieve a final mean A1C of 6.61%. For those on pioglitazone, there were 80 subjects with a mean baseline A1C of 7.69% and a mean decrease from baseline A1C of 1.06% to achieve a final A1C of 6.61%.

Summary of Long-Term Efficacy Data

Both analyses, using either LOCF or available data at time points (observed data), showed that those subjects who remained on muraglitazar 5 mg or 1.5 mg demonstrated a

reduction in A1C from baseline at Week 24 that was generally maintained over a 2 year time period. The differences in the final A1C values for the 2 types of analyses performed are a result of the increasingly strict titration criteria mandated by the protocol over the LT phase. As a result, subjects included in the observed analysis across all treatment arms were those who met the stricter glycemic criteria, were not titrated or discontinued (responders) and therefore, had similar final A1C values.

7.8 Summary of Efficacy

Muraglitazar treatment produced effects on glycemic, lipid and other metabolic endpoints in a dose dependent manner. For the 2.5 mg and 5 mg doses, each consistently demonstrated statistically significant and clinically meaningful changes in multiple glycemic and lipid parameters across the phase 2 and 3 studies when used as monotherapy or in combination with either glyburide or metformin (Table 7.8). Muraglitazar 5 mg in combination with metformin was significantly more effective than pioglitazone 30 mg plus metformin in lowering A1C at 24 weeks of therapy with even larger decreases in A1C observed at 50 weeks. The sustained, durable effect of muraglitazar was further demonstrated in the LT phase of the dose-ranging study, where 88 subjects randomized to muraglitazar 5 mg remained on this dose and achieved a mean A1C < 7%, after 2 years (Study CV168006LT analysis). In addition, the majority of subjects receiving muraglitazar at dose of 2.5 mg or 5 mg in monotherapy or in combination therapy were able to achieve an A1C of < 7%. Treatment with muraglitazar resulted in clinically meaningful improvements in fasting plasma glucose (FPG) and fasting insulin across all studies with improvement in insulin sensitivity (HOMA-IR) and beta cell function (HOMA-%B) observed in the monotherapy study (CV168018).

Muraglitazar-treated subjects demonstrated consistent and clinically meaningful lowering of TG and increases in HDL-C across the Phase 2 and Phase 3 studies, as well as reductions in apoB and non-HDL-C along with neutral effects on LDL-C and likely improvements in LDL particle size. For all studies the primary assessment point for lipids (12 weeks) allowed for evaluation of lipid lowering effects without the confounding effects of subjects starting or changing other lipid-modifying therapies such as statins or fibrates. In addition, muraglitazar 5 mg plus metformin was significantly more effective in improving TG, apoB, non-HDL-C and HDL-C compared to pioglitazone 30 mg plus

metformin. The observed improvements in lipid parameters were maintained throughout the studies beyond the Week 12 assessment point. Lastly, muraglitazar treatment resulted in improvements in several surrogate markers, including decreases in the inflammatory marker, hs-CRP, and thrombotic markers, PAI-1 and fibrinogen across all studies.

The benefits of muraglitazar 2.5 and 5 mg as monotherapy and as combination therapy in the treatment of type 2 diabetes are clinically meaningful and are substantiated by:

- Large and clinically significant reductions in A1C and FPG levels at the 2.5 mg and 5 mg doses of muraglitazar (all 5 pivotal studies).
- Very large reductions (-2.6%) in A1C in diabetic subjects with high baseline A1C levels (> 10.0% and ≤ 12.0%) at the 5 mg dose of muraglitazar in the open-label cohort of monotherapy study CV168018.
- Achievement of glycemic targets (defined as A1C < 7%) in the majority of subjects (ranging from 52.3% to 71.8%) at the 2.5 mg and 5 mg doses of muraglitazar (all studies).
- Sustained efficacy as shown by maintenance of reduced A1C to levels below glycemic goals for at least 2 years in monotherapy study CV168006 and for at least 50 weeks as combination therapy with metformin in study CV168025.
- Reductions in several metabolic indicators of insulin resistance (fasting insulin, fasting C-peptide, and FFA levels) (all studies).

Table 7.8: Phase 3 Efficacy Results - Key Glycemic and Lipid Parameters - Type 2 Diabetics

Study Number	Glycemic Parameter[a]	Mean Change From Baseline: Week 24 Glycemic Results				Lipid Parameter[a]	Mean Percent Change From Baseline: Week 12 Lipid Results			
		Muraglitazar mg: 2.5	Muraglitazar mg: 5	Placebo	Pioglitazone		Muraglitazar mg: 2.5	Muraglitazar mg: 5	Placebo	Pioglitazone
Monotherapy Studies:										
CV168006	A1C	--	-1.18	--	-0.57[b]	TG	--	-21.10	--	-9.25[b]
	FPG	--	-40.40	---	-22.49[b]	HDL-C	--	+17.37	--	+10.01[b]
CV168018	A1C	-1.05	-1.23	-0.32	--	TG	-17.93	-27.44	-1.72	--
	FPG	-25.61	-32.76	+1.07	--	HDL-C	+9.64	+16.10	+2.43	--
Combination Study with Sulfonylurea:										
CV168021	A1C	-1.00	-1.21	+0.16	--	TG	-13.87	-26.12	+3.18	--
	FPG	-26.74	-35.96	+11.59	--	HDL-C	+7.37	+13.72	-0.24	--
Combination Studies with Metformin:										
CV168022	A1C	-0.91	-1.16	-0.05	--	TG	-13.88	-29.20	+3.22	--
	FPG	-25.56	-35.16	-2.12	--	HDL-C	+8.00	+14.14	+0.95	--
CV168025	A1C	--	-1.14	--	-0.85[c]	TG	--	-28.43	--	-14.44[c]
	FPG	--	-43.52	--	-32.69[c]	HDL-C	--	+19.16	--	+13.61[c]

[a] Units for glycemic & lipid parameters: A1C - (%); FPG, TG & HDL-C - (mg/dL)

[b] Pioglitazone 15 mg

[c] Pioglitazone 30 mg

8 PHASE 2 AND 3 CLINICAL STUDIES - SAFETY

8.1 Overview

The muraglitazar clinical development program includes 5128 subjects with type 2 diabetes treated with either muraglitazar or a comparator: 808 subjects in Phase 1 clinical pharmacology studies, 1477 subjects in a Phase 2 clinical study, and 2843 subjects in Phase 3 clinical studies.

Assessment of the safety of muraglitazar is based primarily on 5 Phase 2/Phase 3 studies (CV168006, CV168018, CV168021, CV168022, and CV168025) with 4320 treated subjects (2969 on muraglitazar and 1351 on comparator). One of these studies (CV168006) also has safety data presented based on LT exposure (≥ 2 years) with 593 subjects who received muraglitazar treatment for at least 104 weeks. A total of 2344 subjects with type 2 diabetes in the Phase 2 and Phase 3 studies received muraglitazar 2.5 mg or 5 mg doses (the proposed doses).

As stated in Section 1, the safety data in subjects with type 2 diabetes from the Phase 2 and Phase 3 studies with muraglitazar is presented utilizing 2 different datasets in order to assess the safety data in the most meaningful manner:

1) the "NDA Dataset" (data submitted to the FDA in December 2004).
   a) Mostly used for safety data summarized based on the 24-week data from the Phase 2/3 program by dose, to allow an assessment of the quantitative differences of drug effects relative to the control groups, eg edema incidence, amount of weight gain.
2) the "Complete Dataset" (data from the NDA Dataset plus the 120 Day Safety Update submitted to the FDA in April 2005 and additional data for clinically important events from the long-term phase of studies CV168006, CV168021, CV168022, and CV168025). *(Note: This dataset includes safety information that may not be incorporated in the Agency's analysis)*
   a) Mostly used for infrequent events and presented as total muraglitazar experience in subjects with type 2 diabetes across the entire muraglitazar dose range

Additional analyses are presented whenever these were deemed appropriate for a better understanding of the short- and LT safety profile of muraglitazar.

For each data presentation in this document where data is pooled across studies, it will be indicated whether the NDA Dataset or the Complete Dataset is used.

Safety data from the study in non type 2 diabetics (CV168008) can be found in Attachment 3.1A (ST data) & Attachment 3.1B (LT data).

The following data presentations are provided in this document:

1) **Common Adverse Events** (AEs), **discontinuations due to AEs**, and **Serious Adverse Events** were analyzed using data from the 24-week Phase 3 studies (018, 021, 022, and 025) and are presented by dose (NDA dataset)
2) **Deaths, all cancers, and bladder cancers** were analyzed for all Phase 2 and 3 subjects and pooled according to treatment: placebo, muraglitazar (all doses), and pioglitazone (all doses) and are presented as Kaplan-Meier cumulative incidences over time (Complete Dataset)
3) **Cardiovascular Safety** - atherosclerotic cardiovascular events were analyzed for all Phase 2 and 3 subjects using the Complete Dataset and pooled according to treatment: placebo, muraglitazar (all doses), and pioglitazone (all doses) and are presented as Kaplan-Meier cumulative incidences over time. Events of heart failure were analyzed using data from the 24-week Phase 2/3 studies (006, 018, 021, 022, and 025) and are presented by dose (NDA Dataset). In addition, events of heart failure were analyzed for all Phase 2 and 3 subjects using the Complete Dataset and presented by dose for the monotherapy-, combination with metformin- and combination with glyburide studies.

Several events of special interest are discussed in more detail:

4) **Edema** - The 24-week edema incidence as well as the percent of subjects discontinuing for edema is presented by treatment and dose for each study (NDA Dataset)
5) **Weight Gain** - The change in body weight at 24 weeks using LOCF is presented by treatment and dose for each study (NDA Dataset)
6) **Hematologic Parameters** - The 24-week incidence of anemia, and the mean change from baseline in hemoglobin, hematocrit, leukocytes, and ANC at week 24 will be presented pooled for monotherapy and combination therapy. The 104-week incidence of anemia, and the mean change from baseline in hemoglobin, hematocrit, leukocytes, and absolute neutrophil counts (ANC) at week 104 will be presented for the dose ranging monotherapy study (NDA dataset). The occurrence

of ANC < 1000 cells/µl on 2 consecutive visits will be reported for the NDA dataset.

7) **Hypoglycemia** - The percent of subjects with symptoms of hypoglycemia and a glucose level ≤ 50 mg/dL as determined by fingerstick is presented by treatment and dose for each study (NDA Dataset)
8) **Renal Safety - s**erum creatinine levels - the mean change from baseline at 24 weeks in serum creatinine levels are presented by treatment and dose for each study (NDA Dataset)
9) **Hepatobiliary Safety -** liver function tests and cholelithiasis - Liver safety was evaluated by analyzing the mean change from baseline at 24 weeks in ALT across the Phase 2 and three studies, pooling all muraglitazar and pioglitazone doses (NDA Dataset). In addition the percentage of subjects meeting predefined thresholds for ALT and bilirubin was also analyzed using the Complete Dataset
10) **Muscle Safety** - Muscle safety was evaluated by analyzing the mean change from baseline at 24 weeks across the Phase 2 and 3 studies pooling all muraglitazar doses of 5 mg and lower and all pioglitazone doses (NDA Dataset). The results for the muraglitazar 10 and 20 mg doses are separately presented. The results are presented for those subjects taking a statin at baseline and those not taking a statin at baseline. In addition, the percentage of subjects meeting predefined CK thresholds is also presented by statin use at baseline using the Complete Dataset.

Data Not Pooled for the Safety Analysis Presented in This Document

Non-diabetic subjects with mixed dyslipidemia in Study CV168008: The data from Study CV168008 are not included in the integrated analyses.

Phase 1 studies: The safety data from Phase 1 studies (including a small in-patient 28-day, dose-ranging study in subjects with type 2 diabetes [Study CV168002]) are presented separately in Section 5 of this document.

8.2 Extent of Exposure

This paragraph details the extent of exposure on muraglitazar that formed the basis of the safety evaluations. For completeness, the exposure on muraglitazar in subjects with mixed dyslipidemia is also provided. The extent of exposure for both the NDA and the Complete Dataset are provided.

The muraglitazar NDA contained data on a total 2969 subjects with type 2 diabetes and 257 non-diabetic subjects with mixed dyslipidemia who were treated with muraglitazar in Phase 2 and Phase 3 clinical studies. The majority of subjects received muraglitazar treatment for at least 24 weeks. The individual study protocols permitted a ± 3 day window for the Week 24 visit. Therefore, the subjects completing the study at Week 24 are spread between the duration categories of 12 to < 24-week and ≥ 24 to < 36 week in Table 8.2A. Of these, 697 subjects received muraglitazar treatment for at least 104 weeks during the LT extension phase of the dose ranging study.

Table 8.2A: Extent of Exposure to Muraglitazar, All Muraglitazar-treated Subjects in Phase 2 and 3 Studies (NDA Data Set)

Duration (weeks):	Any MUR Dose Diabetic Subjects N =2969	Any MUR Dose Mixed Dyslipidemic Subjects N = 257	Any MUR Dose Total N =3226
< 12	380(12.8)	77(30.0)	457(14.2)
12 - <24	702(23.6)	28(10.9)	730(22.6)
24 - <36	1088(36.6)	16(6.2)	1104(34.2)
36 - <48	39(1.3)	10(3.9)	49(1.5)
48 - <60	37(1.2)	9(3.5)	46(1.4)
60 - <72	31(1.0)	3(1.2)	34(1.1)
72 - <84	16(0.5)	4(1.6)	20(0.6)
84 - <96	23(0.8)	6(2.3)	29(0.9)
96 - <104	60(2.0)	0	60(1.9)
104 - <114	456(15.4)	104(40.5)	560(17.4)
114 - <126	130(4.4)	0	130(4.0)
>= 126	7(0.2)	0	7(0.2)
Duration (weeks):			
Mean (SD)	42(38.0)	56(45.6)	43(38.8)
Median	24	43	24
Range	0 - 132	0 - 111	0 - 132

Data set: Treated Subjects and Open-Label Cohort
N = number of Treated or Open-Label Cohort Subjects

Since the submission of the muraglitazar NDA data from several studies have become available: The CV168025 study (TZD comparator) has completed providing an additional 6 months of data. In addition, analyses of the ongoing studies, CV168006 (dose ranging) CV168021 (combination with glyburide) and CV168022 (combination with metformin) were performed providing additional LT data. The total exposure to muraglitazar available in the Complete Dataset is presented in Table 8.2B.

The total exposure on muraglitazar, calculated as patient years of experience for subjects with type 2 diabetes, was 516 years for the muraglitazar 2.5 mg dose, 1589 years on the 5 mg dose and a total of 1168 patient years on the 10 and 20 mg dose; the total muraglitazar exposure was 3760 years.

Table 8.2B: Extent of Exposure to Muraglitazar, All Muraglitazar Treated Subjects in Phase 2 and 3 Studies (Complete Dataset)

Duration (weeks):	Any MUR Dose Diabetic Subjects N =3125	Any MUR Dose Mixed Dyslipidemic Subjects N = 257	Any MUR Dose Total N =3382
< 12	457(14.6)	77(30.0)	534(15.8)
12 - <24	323(10.3)	28(10.9)	351(10.4)
24 - <36	486(15.6)	16(6.2)	502(14.8)
36 - <48	140(4.5)	10(3.9)	150(4.4)
48 - <60	480(15.4)	9(3.5)	489(14.5)
60 - <72	282(9.0)	3(1.2)	285(8.4)
72 - <84	260(8.3)	4(1.6)	264(7.8)
84 - <96	37(1.2)	6(2.3)	43(1.3)
96 - <104	10(0.3)	0	10(0.3)
104 - <114	22(0.7)	104(40.5)	126(3.7)
114 - <126	14(0.4)	0	14(0.4)
126 - <138	436(14.0)	0	436(12.9)
138 - <150	157(5.0)	0	157(4.6)
>= 150	21(0.7)	0	21(0.6)
Duration (weeks):			
Mean (SD)	58(45.2)	56(45.6)	58(45.2)
Median	50	43	50
Range	0 - 158	0 - 111	0 - 158

Data set: Treated Subjects and Open-Label Cohort
N = number of Treated or Open-Label Cohort Subjects

8.3 Characteristics of Study Population

8.3.1 Demographic and Other Characteristics of Study Population

A total of 2969 subjects with type 2 diabetes were treated with muraglitazar in Phase 2 and Phase 3 clinical studies. Approximately half of the subjects with type 2 diabetes received muraglitazar as monotherapy (1560 of 2969, 52.5%) and the other half were treated with muraglitazar in combination with glyburide or metformin (1409 of 2969, 47.5%).

Demographic and baseline characteristics were generally well balanced across the muraglitazar, placebo, and pioglitazone treatment groups (Attachment 8.3.1A). There were no meaningful differences among the treatment groups with regard to age, gender, race, or ethnicity. With respect to the safety assessments, there were no meaningful differences in the demographic and baseline characteristics among different treatment arms within each group. Demographic and baseline characteristics were also similar for the monotherapy and combination therapy study populations, with the exception of the median duration of diabetes which was 1.5 years in the monotherapy studies and 5.0 years in the combination studies.

Approximately 15% of the subjects were ≥ 65 years of age and the mean age was 54 years. Both genders were equally represented. Approximately 7% of subjects worldwide were Black, while the percentage of Black subjects in the cohort enrolled in the US was 12%, similar to the national demographic. The Hispanic/Latino ethnicity was well represented between 20 to 35% across the treatment groups.

With the exception of the open label group in the monotherapy study, which had a baseline A1C of 10.6%, the baseline A1C levels of the randomized population were only moderately elevated, around 8%, as typical for a patient population with type 2 diabetes, the mean weight and body mass index were high: around 88 to 91 kg and just above 31, respectively.

Systolic and diastolic blood pressures were on average fairly well controlled: 130 and 80 mmHg respectively (Attachment 8.3.1A).

The lipid profile showed a pattern typical of patients with type 2 diabetes, with elevated triglycerides (200 mg/dL), LDL-C levels in the normal range (130 mg/dL), yet not meeting the National Cholesterol Education Program (NCEP) target of < 100 mg/dL and HDL-C levels in the normal range (45 mg/dL).

A total of 64.7% of subjects with type 2 diabetes had metabolic syndrome at baseline as defined by the NCEP Adult Treatment Panel III guidelines.

Given the importance of lipid management in patients with type 2 diabetes, statins were underused, with 22% of the population on statin therapy at baseline. The use of fibrates was negligible (< 1%).

8.4 Analysis of Adverse Events

In this section, 24-week AE data are presented for the Phase 3 program by dose. Analyses of the 24-week AE data by dose from the Phase 3 program provides a meaningful representation of the events physicians may expect when initiating muraglitazar therapy.

Two types of AEs are excluded from the aggregated presentation of AEs: hypoglycemic events (including the events of symptoms of hypoglycemia accompanied with a fingerstick plasma glucose level ≤ 50 mg/dL) and edema-related AEs. These events are considered separately for the reasons outlined below.

Hypoglycemia events are presented separately from the other AEs in Section 8.5.4. Subjects with type 2 diabetes, who are accustomed to elevated blood glucose levels, may experience symptoms of hypoglycemia after initiation of antidiabetic treatment, even though the blood glucose levels remain within the acceptable range. Therefore, a more careful analysis of these events is warranted to distinguish hypoglycemic symptoms from hypoglycemia that is confirmed by a low glucose level. Accordingly, these events are presented separately from the other AEs.

Edema-related AEs are presented separately from other AEs in Section 8.5.1 for the following reasons:

- Edema-related events are identified based on a predefined list of various Preferred Terms (PT) in the Medical Dictionary for Regulatory Activities (MedDRA). These PTs do not all belong to the same System Organ Classes (SOC) in MedDRA. Therefore, data presentation by SOC and PT do not easily provide an overview of all edema-related events.
- The method used for the data collection of edema-related events was different for Study CV168006 and for Phase 3 studies. In Study CV168006, edema-related events were collected based on the protocol-defined monitoring for events at each visit, whereas in the Phase 3 studies, edema-related events were collected based on spontaneously reported events.

Wherever applicable, a footnote to a table is included to identify whether or not the events of hypoglycemia and edema-related events are included.

8.4.1 Common Adverse Events

In this section data on AEs during the 24-week phase of the Phase 3 trials are presented for doses up to 5 mg by treatment and dose.

Edema-related events were the most commonly reported AEs for muraglitazar; these AEs are discussed in Section 8.5.1.

The overall incidence of AEs with muraglitazar treatment was similar to that with placebo and/or pioglitazone treatment. The most commonly (≥ 5%) reported AEs (excluding hypoglycemic and edema-related AEs) in the monotherapy studies were nasopharyngitis, headache, arthralgia, upper respiratory tract infection, hypertension, diarrhea, and urinary tract infection, with the incidence similar among treatment groups (Table 8.4.1).

Table 8.4.1: Common AEs Reported by >= 5% of Subjects (by PT) During Short-Term/Double-Blind Phase and in the Open-Label Cohort (NDA Dataset)

	Short-term			
PREFERRED TERM (PT) (%)	MUR 2.5 N = 535	MUR 5 N = 1208	PLA N = 528	PIO N = 572
TOTAL SUBJECTS WITH AE	389 (72.7)	812 (67.2)	361 (68.4)	344 (60.1)
NASOPHARYNGITIS	41 (7.7)	85 (7.0)	43 (8.1)	33 (5.8)
HEADACHE	35 (6.5)	75 (6.2)	40 (7.6)	28 (4.9)
ARTHRALGIA	34 (6.4)	73 (6.0)	27 (5.1)	26 (4.5)
UPPER RESPIRATORY TRACT INFECTION	37 (6.9)	69 (5.7)	38 (7.2)	33 (5.8)
HYPERTENSION	29 (5.4)	59 (4.9)	22 (4.2)	32 (5.6)
DIARRHOEA	22 (4.1)	56 (4.6)	28 (5.3)	26 (4.5)
URINARY TRACT INFECTION	32 (6.0)	49 (4.1)	25 (4.7)	24 (4.2)

N = number of Treated or Open-Label Cohort Subjects.
Includes CV168018, 021, 022 and 025 from NDA database.
Non-serious events up to last treatment date of Short-Term/Double-Blind Phase or Open-Label Cohort included.
Serious events up to 30 days post Short-Term/Double-Blind Phase (but prior to Long-Term Phase if any) or Open-Label Cohort included.
All reported hypoglycemic symptoms including the events of confirmed hypoglycemia and edema-related events are excluded from table.
Hypoglycemia and edema-related terms are based upon the muraglitazar predefined list of events.
DATASET: Treated Subjects and Open-Label Cohort MEDDRA VERSION: 7

AEs during 104 weeks of the Dose Ranging study (CV168006)

During the LT phase of the dose ranging study (CV168006) the overall profile of AEs for up to 2 years was consistent with that seen at 24 weeks.

8.4.2 Summary of Premature Discontinuations and Adverse Events Leading to Discontinuation of Study Therapy

In this section data on AEs leading to premature discontinuations of study therapy during the 24-week phase of the Phase 3 trials, and the LT phase of the dose ranging study for doses up to 5 mg are presented (NDA Dataset).

Overall muraglitazar therapy was well tolerated and there were few discontinuations.

During the ST phase of monotherapy or combination therapy studies, the overall incidence of study drug discontinuations was lower for muraglitazar than for pioglitazone or placebo.

The discontinuations due to an AE were slightly higher with muraglitazar than with pioglitazone or placebo. Across the Phase 3 program 3% of subjects discontinued the muraglitazar 2.5 mg dose due to an AE, 4% discontinued the muraglitazar 5 mg dose and 2% each discontinued placebo or pioglitazone 30 mg due to an AE.

Consistent with the ST findings, the overall incidence of study drug discontinuations during the LT phase was lower for muraglitazar than for pioglitazone, because more subjects discontinued due to lack of efficacy on pioglitazone than on muraglitazar. However, a greater proportion of subjects discontinued due to AEs from muraglitazar relative to pioglitazone (muraglitazar ≤ 5 mg: 6% versus pioglitazone ≤ 45 mg: 3%); the AEs leading to discontinuations were similar to those for the ST phase, and the imbalance was mostly caused by a greater frequency of discontinuation due to peripheral edema. None of the AEs leading to discontinuation in the LT phase were unexpected.

Premature discontinuations by study and dose for the 24-week Phase 2 and 3 trials are summarized in Table 8.4.2A and Table 8.4.2B for the LT phase of the dose ranging study (CV168006; NDA Dataset).

Table 8.4.2A: Summary of Premature Discontinuation of Study Medication (ST phase)

	N	No. of subjects discontinued n (%)	Reason for Discontinuation		
			Adverse Event n (%)	Lack of Efficacy n (%)	Other[a] n (%)
Monotherapy					
CV168018					
Mur 2.5 mg	111	21 (19)	3 (3)	9 (8)	9 (8)
Mur 5 mg	114	22 (19)	4 (4)	10 (9)	8 (7)
Pla	115	42 (37)	3 (3)	32 (28)	7 (6)
Mur 5 mg OL	109	48 (44)	4 (4)	27 (25)	17 (16)
Combination with Glyburide					
CV168021					
Mur 2.5 mg + Gly	191	32 (17)	7 (4)	9 (5)	16 (8)
Mur 5 mg + Gly	193	27 (14)	11 (6)	8 (4)	8 (4)
Pla + Gly	199	60 (30)	4 (2)	41 (21)	15 (8)
Combination with Metformin					
CV168022					
Mur 2.5 mg + Met	233	36 (15)	7 (3)	14 (6)	15 (6)
Mur 5 mg + Met	205	26 (13)	9 (4)	7 (3)	10 (5)
Pla + Met	214	63 (29)	4 (2)	33 (15)	26 (12)
CV168025					
Mur 5 mg + Met	587	65 (11)	15 (3)	18 (3)	32 (5)
Pio 30 mg + Met	572	90 (16)	8 (1)	36 (6)	46 (8)

[a] Other includes subject withdrew consent, death, lost to follow-up, poor/non-compliance, pregnancy, subject no longer meets study criteria, administrative reason by the Sponsors, and other

Table 8.4.2B: Summary of Premature Discontinuation of Study Medication, LT Monotherapy

Study	N	No. of subjects discontinued n (%)	Reason for Discontinuation		
			Adverse Event n (%)	Lack of Efficacy[a] n (%)	Other[b] n (%)
Non-titrated Dose					
Mur 1.5 mg	75	23 (31)	8 (11)	1 (1)	14 (19)
Mur 5 mg	108	28 (26)	10 (9)	0	18 (17)
Initial or Titrated Dose					
Any Mur ≤ 5 mg	459	74 (16)	26 (6)	3 (1)	45 (10)
Any Pio ≤ 45 mg	146	52 (36)	5 (3)	30 (21)	17 (12)

[a] Subjects on muraglitazar 5 mg with poor glycemic control may have been titrated to the next available dose, whereas subjects on pioglitazone 45 mg were discontinued. Therefore, lack of efficacy does not include subjects who needed titration.

[b] Other includes subject withdrew consent, death, lost to follow-up, poor/non-compliance, pregnancy, subject no longer meets study criteria, administrative reason by Sponsors, and other.

8.4.3 Serious Adverse Events

In this section, data on serious adverse events (SAEs) during the 24-week phase of the Phase 3 trials and the 104 week period of the dose ranging trial are presented (NDA dataset) (Table 8.4.3A and Table 8.4.3B, respectively).

Table 8.4.3A: SAEs Reported in Subjects During Short-Term/Double-Blind Phase and in the Open-Label Cohort from Phase 3 Studies (NDA Dataset)

	Short-term			
	MUR 2.5 N = 535	MUR 5 N = 1208	PLA N = 528	PIO N = 572
TOTAL SUBJECTS WITH AE	26 (4.9)	53 (4.4)	16 (3.0)	15 (2.6)

N = number of Treated or Open-Label Cohort Subjects.

Detailed results are presented below by grouping.

SAEs during 24-week phase of the Phase 3 Trials

The overall incidence of SAEs during the ST phase was higher for muraglitazar (5% on 2.5 mg and 4% on 5 mg) than placebo or pioglitazone (3% each, Table 8.4.3A). The most common cause for a SAE was due to CV-related events (see Section 8.4.6 for a full discussion of CV safety). Other common causes of SAEs, at a lower incidence rate, were:

- hypoglycemia (2 events on muraglitazar 2.5 mg, 1 event on muraglitazar 5 mg)
- diabetic neuropathy (2 events on muraglitazar 2.5 mg) and
- subcutaneous abscess (2 events on placebo).

SAEs during 104 weeks of the dose ranging study (NDA dataset)

The overall incidence of SAEs during the combined ST and LT phase was higher for muraglitazar (11.8%) than for pioglitazone (9.6%). The SAEs in the 2 treatment groups were ≥ 1.0% in several SOCs as displayed in Table 8.4.3B. The incidence of cardiovascular disorders was higher on muraglitazar than on pioglitazone. An overall evaluation of atherosclerotic cardiovascular events is further presented in Section 8.4.6.

Table 8.4.3B: Number (%) of Subjects with Serious Adverse Events (≥ 1 %): LT Monotherapy (CV168006; NDA Dataset)

System Organ Class	Muraglitazar ≤ 5 mg (Initial or titrated dose) N = 459	Pioglitazone ≤ 45 mg (Initial or titrated dose) N = 146
Cardiac Disorders	12 (2.6%)	2 (1.4%)
Gastrointestinal Disorders	8 (1.7%)	4 (2.7%)
Neoplasms Benign, Malignant, and Unspecified	6 (1.3%)	3 (2.1%)
Renal and Urinary Disorders	5 (1.1%)	1 (0.7%)
Vascular Disorders	5 (1.1%)	0 (0)

8.4.4 Deaths and Noncardiovascular Mortality

A total of 21 deaths due to any cause was reported for subjects with type 2 diabetes across all doses in the Complete Dataset (See Table 8.4.4.1 and Attachment 8.4.4 for a listing of all deaths):

- Eighteen subjects (0.58%) in the muraglitazar monotherapy or combination therapy groups (n = 3125)
- Two subjects (0.24%) in the pioglitazone ≤ 45 mg group (n = 823)
- One subject (0.19 %) in the placebo group (n=528).

None of the deaths reported for muraglitazar-treated subjects was considered by the investigator to be related to the study drug.

Incidence rates have limitations in their interpretation. Incidence rates neither address differences in duration of follow-up among treatments or patterns with which subjects discontinue treatments or are lost to follow-up. To better address the impact of such critical factors, Kaplan-Meier estimates with their corresponding 95% confidence intervals (CI) were calculated for the cumulative incidence of overall mortality across all muraglitazar doses, all pioglitazone doses and placebo. The limited number of subjects followed in the placebo and pioglitazone arms beyond 18 months require that the Kaplan-Meier estimates calculated beyond 18 months be viewed cautiously. The Kaplan-Meier cumulative incidences are provided at 6-month intervals for muraglitazar, placebo and pioglitazone utilizing the complete dataset (Table 8.4.4A).

Table 8.4.4A: Kaplan-Meier Estimate of Cumulative Incidence of All Cause of Death (Complete Dataset)

Time (Month)	Any MUR *			Any PIO =<45			Any PLA **		
	Cum. N of Event	N at Risk	Cumulative Incidence (95% CI)	Cum. N of Event	N at Risk	Cumulative Incidence (95% CI)	Cum. N of Event	N at Risk	Cumulative Incidence (95% CI)
0 - 6	8	2969	0.3 (0.1 - 0.5)	1	823	0.1 (0.0 - 0.4)	0	528	0.0 (0.0 - 0.0)
> 6 - 12	15	2370	0.7 (0.3 - 1.0)	1	646	0.1 (0.0 - 0.4)	1	371	0.6 (0.0 - 1.7)
>12 - 18	16	1716	0.8 (0.4 - 1.2)	1	496	0.1 (0.0 - 0.4)	1	114	0.6 (0.0 - 1.7)
>18 - 24	17	944	0.9 (0.4 - 1.4)	2	110	1.1 (0.0 - 3.1)	1	35	0.6 (0.0 - 1.7)
>24 - 30	18	653	1.1 (0.5 - 1.6)	2	95	1.1 (0.0 - 3.1)	1	0	0.6 (0.0 - 1.7)
>30 - 36	18	614	1.1 (0.5 - 1.6)	2	88	1.1 (0.0 - 3.1)	1	0	0.6 (0.0 - 1.7)

Dataset: Treated Subjects
Note: Including all death anytime during study and after the last treatment.
* Includes titration and non-titration data on all doses of muraglitazar during ST + LT Phase for CV168006.
** Non-titrated dose only. For CV168021 and CV168022 ST+LT, subjects who were randomized to placebo and titrated to muraglitazar 2.5 mg in the LT phase will have only data on placebo included.
PROGRAM SOURCE: /WWBDM/CLIN/PROJ/CV/168/FDA_ADV/DEV/STATS/DEATH_KM_INCIDENCE3.SAS 27-JUN-2005 13:47

Studies included in this analysis were not designed nor statistically powered to assess differences in mortality. Subjects who discontinued early were not followed-up for their status. The impact of differences in drop out rates on the assessment of mortality can therefore not be assessed.

Given the number of subjects studied and the low incidence of mortality observed for all treatments, the Kaplan-Meier estimates suffer from a high degree of variability. This degree of variability makes it very difficult and potentially flawed to infer differences among treatment groups based on a point estimate.

In conclusion, given the number of subjects in this clinical development program and the similar Kaplan-Meier estimates of the cumulative incidences among the treatment groups, no reliable comparison among treatment groups can be made with respect to the incidence of morality.

8.4.4.1 Non-Cardiovascular Deaths

The 21 subjects with diabetes who died are categorized by cause of death in Table 8.4.4.1.

Table 8.4.4.1 Exposure to Study Drug, Total Deaths, and Deaths by Category All Treatment Groups - Complete Dataset

	Muraglitazar					Pioglitazone	Placebo
	1.5	**2.5**	**5**	**10**	**20**		
Subject - Years of Exposure	414	516	1515	623	343	771	333
Cardiovascular		1	7		1		1
Cancer	2	1	4			1	
Other			1	1		1	
Deaths (total)	2	2	12	1	1	2	1

The cardiovascular deaths are described in detail in Section 8.4.6.4. Brief capsule summaries of the deaths due to cancer and other causes are provided below.

Cancer Death All Treatment Groups - Complete Dataset

Muraglitazar 1.5 mg

- Muraglitazar 1.5 mg
  - Subject CV168006-255-1 was a 69-year old Hispanic male with a 4 year history of diabetes and history of anaplastic stomach cancer treated surgically 4 years previously, peripheral vascular disease, obesity, alcohol use, and previous cigarette use. On study day 476 he was hospitalized with asthenia, tiredness, a 10 lb. weight loss and "wasting syndrome." Multiple pulmonary endobronchial masses, liver abnormalities and splenomegaly were identified. This was diagnosed as pulmonary carcinoma unrelated to his previous malignancy. He died on study day 505. The investigator considered the event not likely related to study medication.
  - Subject CV168006-267-5 was a 69-year old white female with a 6-month history of diabetes and history of hypertension, mixed dyslipidemia, and alcohol use. On study day 537 the subject was diagnosed with severe acute myeloid leukemia. She died 6 weeks later. The investigator considered the event not likely related to study medication.

Muraglitazar 2.5 mg

- Muraglitazar 2.5 mg/Metformin 1500 mg
  - Subject CV168006-250-15 was a 51-year old Hispanic male with a 3 year history of diabetes and history of retinopathy and tobacco use. On study day 189 the subject presented with abdominal pain. A CT scan showed an enlarged liver with multiple nodular lesions. A liver biopsy on study day 210 revealed well differentiated hepatocellular carcinoma. The subject died on study day 224. The investigator considered the event not likely related to study medication.

Muraglitazar 5 mg

- Muraglitazar 5 mg
  - Subject CV168006-80-9 was a 70-year old white female with a 2 year history of diabetes and history of chronic obstructive pulmonary disease, current cigarette use, bronchitis, hypertension, obesity, deep vein thrombosis, hypercholesterolemia, osteoporosis, arthritis, and alcohol use. Worsening fatigue, bronchitis and shortness of breath prompted a CT scan of the chest on study day 752 which revealed a lung tumor, nodules throughout the liver, and mediastinal

and hilar adenopathy. The subject died on study day 808. The investigator considered the event not likely related to study medication.

- Muraglitazar 5 mg/Metformin 2000mg
  - Subject CV168022-142-4 was a 63-year old white female with a 10 year history of diabetes and history of hypercholesterolemia, hypertriglyceridemia, nodular goiter, osteoporosis, and prior tobacco use for 35 years. The subject presented with altered mental status on study day 206 and was found to have small cell cancer of the lung with metastasis to brain, adrenal and liver. The subject died on study day 326. The investigator considered the event not likely related to study medication.
- Muraglitazar 5 mg/Metformin 1500mg
  - Subject CV168022-256-6 was a 56-year old Hispanic female with a 10 year history of diabetes and history of cancer of the breast 12 years previously, hypertension, obesity, mixed dyslipidemia, diabetic retinopathy and current tobacco use. On study day 27 a bone scan was performed due to a back pain which had been present prior to randomization. The bone scan revealed multiple osseous metastases of breast cancer. The subject died on study day 149. The investigator considered the event not likely related to study medication.
- Muraglitazar 5 mg/Metformin 2500mg
  - Subject CV168025-288-65 was a 50-year old female with an 11 year history of diabetes and history of hypertension and obesity. On study day 114 the subject had nausea, abdominal pain, jaundice and choluria. She had elevations of bilirubin, ALT and AST, and alkaline phosphates. A CT scan revealed a liver lesion and a biopsy on study day 176 revealed a metastatic lesion from a pancreatic carcinoma. The subject died on study day 220. The investigator considered the event not likely related to study medication.

Pioglitazone

- Pioglitazone 15 mg
  - Subject CV168006-10-1 was a 66-year old white male with a 2 month history of diabetes and history of hypertension, hypercholesterolemia, cirrhosis, jaundice and cigarette smoking for 45 years. The subject was diagnosed with throat cancer on study day 647. He died on study day 716. The investigator considered the event not likely related to study medication.

Other Deaths All Treatment Groups - Complete Dataset

Muraglitazar 5 mg

- Muraglitazar 5 mg/Glyburide 15 mg
  - Subject CV168021-29-21 was a 44-year old white male with a 3 year history of diabetes and history of overweight, hypercholesterolemia and impotence. On study day 29 the subject died as the result of a gun shot wound.

Muraglitazar 10 mg

- Muraglitazar 10 mg
  - Subject CV168006-5-3 was a 62-year old white female with a history of hypertension, smoking and alcohol use. On study day 112 she died in a motor vehicle accident. Her car was stopped at a light when struck by a truck. The investigator considered the event not likely related to study drug.

Pioglitazone

- Pioglitazone 30 mg/Metformin 2500 mg
  - Subject CV168025-242-29 was a 67-year old white male with a 13 year history of diabetes and history of obesity, hypertension, diabetic neuropathy, diabetic retinopathy, and current tobacco use. On study day 36 the subject was hospitalized with urolithiasis and had surgery. On day 39 the subject had a acute perforated duodenal bulb ulcer and died. The investigator considered the event not related to study drug.

8.4.5 Malignant Neoplasm

There were 44 subjects with 46 events of cancer in the Complete Dataset. A total of 34 subjects with 36 events of cancer were reported on muraglitazar (6 on muraglitazar 1.5 mg, 5 on muraglitazar 2.5 mg, 19 on muraglitazar 5 mg, 5 on muraglitazar 10 mg, and 1 on muraglitazar 20 mg, generally reflecting the exposure to each dose in the program). There were 9 subjects with 9 cancer events on pioglitazone and 1 cancer event on placebo.

No pattern of tumor types was identified. The most frequent tumor types reported on muraglitazar were basal cell, lung, and prostate cancer with 5 events each. Four events of

breast cancer and 3 events of pancreatic cancer were reported. The most frequent tumor type seen on pioglitazone was prostate cancer (4 events).

Of the 36 events of cancer in the muraglitazar group:

- 13 were reported within 90 days of initiation of study drug
- 3 additional events within 180 days of initiation of study drug
- 11 additional events within 1 year of initiation of study drug
- 6 additional events within 2 years of initiation of study drug
- 3 additional events within 3 years of initiation of study drug

Four events of bladder cancer were reported in the program, 2 on muraglitazar and 2 on pioglitazone. The 2 events of bladder cancer on muraglitazar occurred in the muraglitazar 10 mg treatment group in the dose ranging study:

- one occurred on Day 58 in a white male 71 years of age with type 2 diabetes and a history of cigarette smoking. Significant papillary transitional cell carcinoma was diagnosed and resected. The pathology report stated findings consistent with low grade papillary neoplasm without stoma invasion. This event was considered a recurrence of a bladder cancer diagnosed 26 years prior to study entry.
- one event occurred on Day 573 in a white male aged 66 with a history of cigarette smoking. This subject had microscopic hematuria at baseline and a recurrence of microscopic hematuria on Day 245. Abiopsy taken on Day 573 revealed high grade urothelial carcinoma which was resected.

The 2 events of bladder cancer on pioglitazone occurred in 2 subjects on pioglitazone 15/45mg and 30mg. One of these events was a recurrence. No events of bladder cancer were reported in the placebo group.

Table 8.4.5A presents the incidence per 1000 patient years of exposure for the different treatment groups. The incidence per 1000 patient years of exposure seen for any muraglitazar is lower than that of pioglitazone. Table 8.4.5B presents the Kaplan-Meier estimate of cumulative incidence. One event occurring after titration from placebo to muraglitazar 2.5 mg is not included in the Kaplan-Meier estimate.

In addition to the 44 cases of cancer discussed above, 6 cases of thyroid neoplasm and 1 event of neoplasm skin were reported. The thyroid neoplasms were recorded based on the coding in MedDRA Version 7.0 which is coding thyroid nodules into the PT ‘thyroid neoplasm.’ All of these events were considered benign by the investigator. The event of

neoplasm skin was reported as an AE of "benign tumor of the head" which was surgically excised and didn't require follow-up. However, the pathology report was unavailable. All events of cancer as well as these 6 events are listed in Attachment 8.4.5.

Table 8.4.5A: Incidence of Malignant Neoplasm-related AEs per 1,000 Patient Years of Exposure - CV168006 ST+LT, 018 DB+OL, 021 ST+LT and 022 ST+LT and 025 ST+LT Combined

	Treatment Exposure			
	ANY MUR =<5 N=2639	ANY MUR N=3125	ANY PIO =<45 N= 823	ANY PLA N= 528
Number of Subjects With at least one Event	29	34	9	1
Total Patient Years of Exposure	2512.1	3471.1	767.91	332.13
Incidence per 1,000 Patient-Years Exposure	11.54	9.80	11.72	3.01

Table 8.4.5B: Kaplan-Meier Estimate of Cumulative Incidence of Malignant Neoplasm-Related AEs - CV168006 ST+LT, 018 DB+OL, 021 ST+LT, 022 ST+LT and 025 ST+LT

	Any MUR *			Any PIO =<45			Any PLA **		
Time (Month)	Cum. N of Event	N at Risk	Cumulative Incidence (95% CI)	Cum. N of Event	N at Risk	Cumulative Incidence (95% CI)	Cum. N of Event	N at Risk	Cumulative Incidence (95% CI)
0 - 6	15	2969	0.5 (0.3 - 0.8)	2	823	0.3 (0.0 - 0.7)	1	528	0.2 (0.0 - 0.6)
> 6 - 12	24	2359	1.0 (0.6 - 1.4)	6	645	1.0 (0.2 - 1.8)	1	371	0.2 (0.0 - 0.6)
>12 - 18	29	1707	1.5 (0.9 - 2.0)	7	492	1.9 (0.0 - 3.7)	1	114	0.2 (0.0 - 0.6)
>18 - 24	30	938	1.6 (1.0 - 2.2)	9	109	3.7 (0.6 - 6.9)	1	35	0.2 (0.0 - 0.6)
>24 - 30	32	650	1.9 (1.1 - 2.6)	9	93	3.7 (0.6 - 6.9)	1	0	0.2 (0.0 - 0.6)
>30 - 36	33	610	2.1 (1.2 - 2.9)	9	86	3.7 (0.6 - 6.9)	1	0	0.2 (0.0 - 0.6)

8.4.6 Cardiovascular Events and Mortality

Several clinical markers for cardiovascular (CV) risk, including A1C, HDL-C, Apo-B, and inflammatory markers, are all favorably affected by muraglitazar. Experimental data demonstrate favorable effects of muraglitazar on macrophage function and markers of thrombogenicity. Muraglitazar's preclinical and clinical profile is consistent with a protective effect on atherosclerotic cardiovascular events. Although a planned definitive study to assess the cardioprotective effects of muraglitazar (see Section 9.2.3) will take a greater number of subjects followed for a longer duration than available in the current database, a careful evaluation of atherosclerotic events within the current program was performed.

Summary of Results

The Kaplan-Meier method indicated a comparable cumulative incidence of CV events for muraglitazar-treated (all doses combined) and placebo-treated subjects. Within the muraglitazar treated subjects, the Kaplan-Meier estimates for the cumulative event rates were highest in subjects treated with doses equal to or less than 2.5 mg and lowest for subjects treated with doses equal to or greater than 10 mg (i.e., 10 mg or 20 mg). As the clinical program was not designed to definitively address the incidence of CV events, the 95% confidence intervals around all point estimates for cumulative incidence were wide.

In order to assess the effect of muraglitazar on atherosclerotic CV events (including cerebrovascular events), a list of atherosclerotic CV adverse events from the Cardiac Disorders SOC and Nervous System Disorders SOC (see Attachment 8.4.6A) was compiled at the start of the muraglitazar clinical development program. All adverse events that were coded to the pre-specified terms in this list and all sudden deaths and unexplained deaths were included in the analysis of CV events. Thus the included events encompassed acute athero-thrombotic events as well as chronic atherosclerotic events such as angina and coronary artery disease. It should be noted that heart failure events were compiled and analyzed separately (see Section 8.4.7).

Detailed analyses of CV events are presented using the most complete database available (Complete Dataset). For reference, analyses based on the NDA Dataset are included, but

it should be noted that the Complete Dataset has additional information provided by CV events reported or identified after database lock for the NDA.

Statistical Methods for Analysis of Cardiovascular Safety Profile

To best understand the cardiovascular safety profile of muraglitazar, integrated analyses were performed for CV death and for a pre-defined set of CV events (including CV deaths) which represented artherosclerotic disease. Analyses were performed in several ways to best understand the nature of their relationship with muraglitazar treatment and dose.

Two analyses were performed to describe the rates on muraglitazar relative to that seen with placebo and pioglitazone. For these analyses, doses of muraglitazar were combined as were doses of pioglitazone (i.e. dose was not taken into account).

Analysis 1 - Incidence Rates by Years of Exposure to Treatment

Incidence rates adjusted for subject years of exposure were calculated. For this presentation, the number of subjects with events was divided by the total years of exposure for each treatment. Exposure to treatment for each subject was calculated as the time until their initial event or end of observation, for those subjects who did not have an event. For subjects initially randomized to placebo and who subsequently received muraglitazar, their muraglitazar exposure was included in this presentation provided an early event during placebo treatment had not been observed.

Analysis 2 - Time to Event Analysis

Kaplan Meier estimates and 95% confidence intervals were computed. This analysis used the same population of subjects as in Analysis 1, except that placebo subjects for whom muraglitazar treatment was initiated had their data censored at the time that muraglitazar dosing began. Therefore, data obtained on placebo subjects is not utilized after switching to muraglitazar. The Cox proportional hazards model was also utilized to estimate hazard ratios and their 95% confidence intervals.

Analysis was also performed on the time to first occurrence of CV events to further understand the relationship of these endpoints with respect to treatment and dose of muraglitazar. By design, most studies allowed for a dose titration of muraglitazar for

inadequate glycemic control. Thus, there are limitations in understanding the relationship of CV events to dose, given that dose can be confounded with duration of treatment. To address this, the following analyses were performed.

Subjects were categorized as either having never received muraglitazar or having received ≤ 2.5 mg, 5mg or ≥ 10mg of muraglitazar. The dose of muraglitazar assigned to a subject was the maximum dose received prior to or at the time of the subject's first occurrence of an event. Subjects never receiving muraglitazar included both placebo subjects and subjects randomized to pioglitazone. Subjects who were initially randomized to placebo, but subsequently received muraglitazar, were categorized as muraglitazar subjects for these analyses, if their first event occurred after the switch of treatment to muraglitazar. Thus, these analyses are not based on the treatment to which a subject was initially randomized. In addition, the subjects' dose may in some way be associated with potential for increased risk to these events. Results should be viewed with these limitations in mind.

Kaplan Meier estimates for the endpoints described were computed with their associated 95% confidence interval. A Cox proportional hazards model was utilized to assess both the overall effect of muraglitazar and whether a linear dose response existed. Hazard ratios and their 95% confidence intervals were computed. Significance levels for the Cox model, which tested both for an overall muraglitazar effect and a dose trend are presented, although they were not pre-specified and should be viewed as descriptive.

8.4.6.1 Analysis of Cardiovascular Events: Complete Dataset

Incidence Rates by Years of Exposure to Treatment

Table 8.4.6.1A describes the number of subjects experiencing CV events, and the CV event rate for placebo, pioglitazone, and each dose of muraglitazar. A listing of subjects with CV events is included as Attachment 8.4.6.1A. The data integrated from all studies show a similar event rate for muraglitazar 5 mg and placebo, and a higher event rate for muraglitazar 2.5 mg. The lowest event rate was observed for muraglitazar 10 mg. The lack of a dose response relationship for CV events, seen in data integrated from all studies, was also seen in data from the dose ranging study, CV168006 (a randomized,

within-trial comparison of doses). Additional analyses of CV events were performed using Kaplan-Meier and Cox Regression methods, as described in subsequent sections.

Table 8.4.6.1A: Incidence of CV Events Per 1000 Years of Exposure, Studies 006, 018 DB + OL, 021, 022, 025: Complete Dataset

		MUR 1.5	MUR 2.5	MUR 5	MUR 10	MUR 20	PLA	ANY PIO
CV168006 ST+LT	# of Subjects with at Least One Event	10		7	12	8		5
	Years of Exposure	403.12		508.39	611.65	338.05		324.95
	Subjects/1000 Years	24.81		13.77	19.62	23.67		15.39
CV168018 DB	# of Subjects with at Least One Event		2	2			1	
	Years of Exposure		46.39	48.03			43.84	
	Subjects/1000 Years		43.11	41.64			22.81	
CV168018 OL	# of Subjects with at Least One Event			1				
	Years of Exposure			38.99				
	Subjects/1000 Years			25.65				
CV168021 ST+LT	# of Subjects with at Least One Event		11	13			4	
	Years of Exposure		202.86	204.47			123.61	
	Subjects/1000 Years		54.23	63.58			32.36	
CV168022 ST+LT	# of Subjects with at Least One Event		8	8			6	
	Years of Exposure		261.17	236.00			162.18	
	Subjects/1000 Years		30.63	33.90			37.00	
CV168025 ST+LT	# of Subjects with at Least One Event			15				10
	Years of Exposure			464.99				437.08
	Subjects/1000 Years			32.26				22.88
Total	# of Subjects with at Least One Event	10	21	46	12	8	11	15
	Years of Exposure	403.12	510.42	1500.87	611.65	338.05	329.63	762.03
	Subjects/1000 Years	24.81	41.14	30.65	19.62	23.67	33.37	19.68

Dataset: Treated Subjects and Open-Label Cohort MedDRA Version: 8.0
Includes all cardiovascular-related terms and CV Deaths based upon the muraglitazar predefined list of events.
Non-serious events up 1 day post last treatment day included.
Serious events up to 30 days post last treatment day included.
Years of exposure is the duration of treatment up to the date of the first CV event or CV Death, if applicable
Note: DB = double-blind; OL = open-label

Time to Event Analysis: Kaplan-Meier Estimates

Kaplan-Meier estimates of the cumulative incidence of first events over time with the corresponding 95% confidence intervals were calculated for the three treatment groups (any dose of muraglitazar, any dose of pioglitazone, or placebo using the Complete Dataset, see Table 8.4.6.1B). All doses of muraglitazar were included in this analysis (including the 10 and 20 mg dose) as well as all doses of pioglitazone. Pooling across all doses of muraglitazar in this analysis avoids issues related to assignment of CV events to a particular dose after titration of muraglitazar. Estimates beyond 18 months of treatment should be interpreted cautiously given the small number of subjects in the placebo and pioglitazone treatment groups.

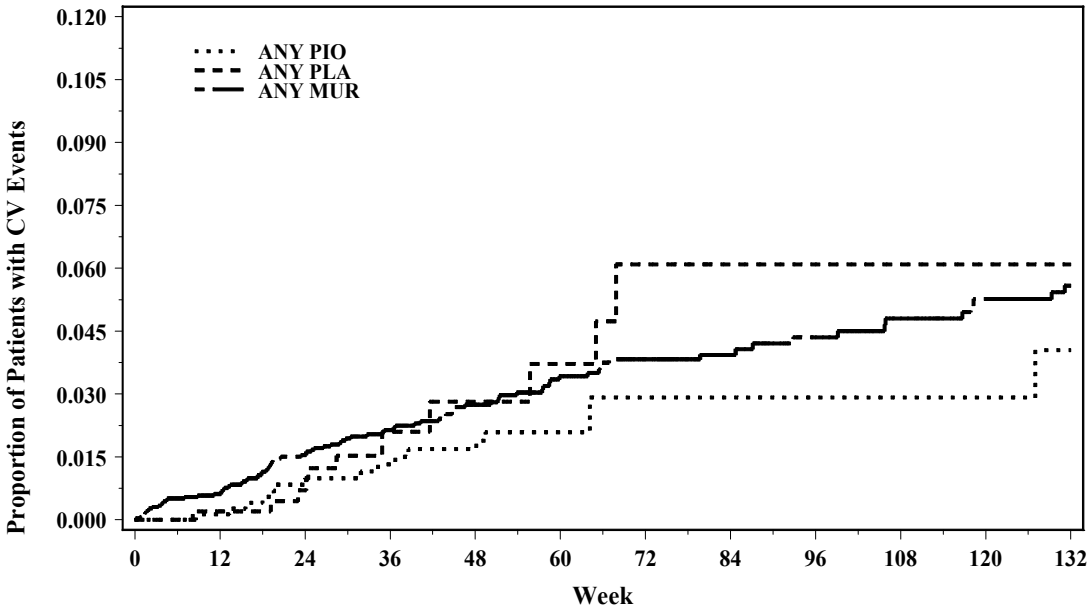
The incidence of CV events was similar across all 3 treatment groups, and the 95% confidence intervals were wide (Table 8.4.6.1B). The highest incidence as of 18 months of follow-up was observed for the placebo treated subjects. A graphic display of the Kaplan-Meier estimate for the three treatment groups is provided in Figure 8.4.6.1A. While Figure 8.4.6.1A is consistent with comparable risk for CV events in muraglitazar-treated subjects and placebo-treated subjects, it should be noted that the muraglitazar development program was not designed to provide a definitive comparison of CV event rates in muraglitazar-treated and placebo-treated subjects.

Table 8.4.6.1B: Kaplan-Meier Estimate of Cumulative Incidence of CV Events, Studies 006, 018 DB + OL, 021, 022, 025: Complete Dataset

	Any MUR *			Any PIO =<45			Any PLA **		
Time (Month)	Cum. N of Event	N at Risk	Cumulative Incidence (95% CI)	Cum. N of Event	N at Risk	Cumulative Incidence (95% CI)	Cum. N of Event	N at Risk	Cumulative Incidence (95% CI)
0 - 6	46	2969	1.7 (1.2 - 2.2)	7	823	1.0 (0.3 - 1.7)	5	528	1.2 (0.2 - 2.3)
> 6 - 12	70	2344	3.0 (2.3 - 3.7)	13	640	2.1 (0.9 - 3.2)	8	366	2.8 (0.7 - 5.0)
>12 - 18	81	1685	3.8 (3.0 - 4.7)	14	485	2.9 (0.9 - 4.9)	11	113	6.1 (1.8 - 10.3)
>18 - 24	86	926	4.5 (3.5 - 5.5)	14	106	2.9 (0.9 - 4.9)	11	33	6.1 (1.8 - 10.3)
>24 - 30	92	638	5.4 (4.2 - 6.7)	15	93	4.0 (1.1 - 7.0)	11	0	6.1 (1.8 - 10.3)
>30 - 36	94	593	6.2 (4.4 - 7.9)	15	85	4.0 (1.1 - 7.0)	11	0	6.1 (1.8 - 10.3)

Dataset: Treated Subjects
Note:Cardiovascular AEs and CV Death are based on the Muraglitazar Predefined List of AE event preferred terms. It includes all Investigator-Identified CV-related AEs and deaths up to 1 days post-treatment and up to 30 days post-treatment for SAE.
* Includes titration and non-titration data on all doses of muraglitazar during ST + LT Phase for CV168006.
** Non-titrated dose only. For CV168021 and CV168022 ST+LT, subjects who were randomized to placebo and titrated to muraglitazar 2.5 mg in the LT phase will have only data on placebo included.
PROGRAM SOURCE: /WWBDM/CLIN/PROJ/CV/168/FDA_ADV/DEV/STATS/CV_CVDTH_KM_INCIDENCE.SAS 5-AUG-2005 07:01
Note: DB = double-blind; OL = open-label

Figure 8.4.6.1A: Kaplan-Meier Estimates for Time to First CV Event by Treatment, Studies 006, 018 DB + OL, 021, 022, 025: Complete Dataset

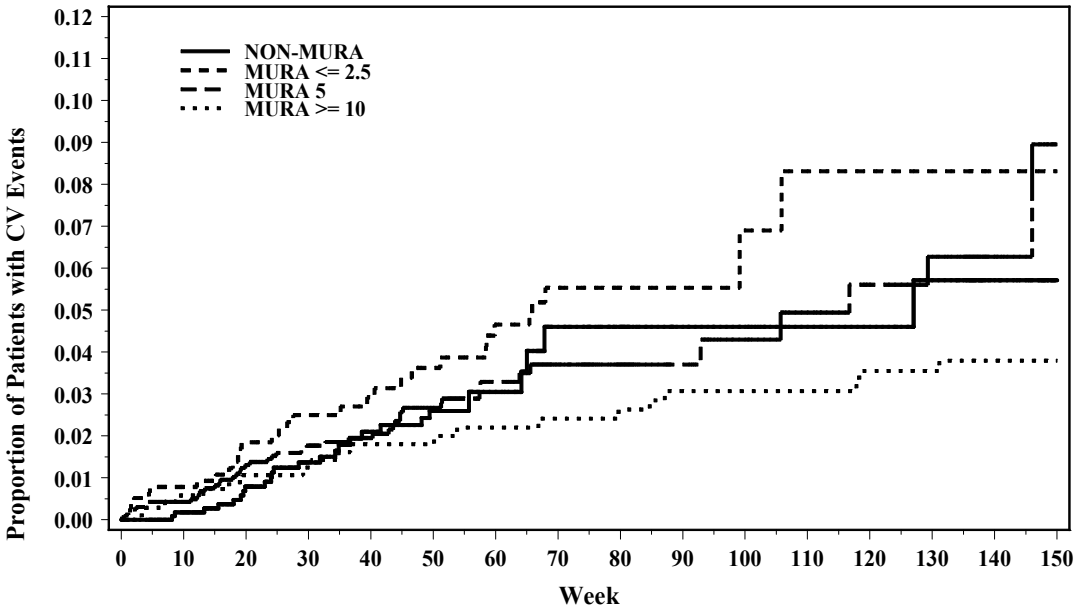


N at risk												
ANY PIO	823	768	655	552	493	121	108	106	100	92	90	85
ANY PLA	528	483	378	164	130	107	54	2	0	0	0	0
ANY MUR	2969	2741	2394	1877	1710	1228	994	698	649	633	607	591

Note: DB = double-blind; OL = open-label

An additional Kaplan-Meier analysis was performed to characterize the effect of dose of muraglitazar on cumulative incidence of CV events. Subjects were categorized as either having never received muraglitazar (non-mura) or having received ≤ 2.5 mg, 5 mg, or ≥ 10 mg muraglitazar. Subjects never receiving muraglitazar (non-mura) included placebo subjects and subjects randomized to pioglitazone. As shown in Figure 8.4.6.1B, there was no clear relationship of dose of muraglitazar to cumulative incidence of CV events.

Figure 8.4.6.1B: Kaplan Meier Estimates for Time to First CV Event by Treatment, Studies 006, 018 DB + OL, 021, 022, 025: Complete Dataset



N at risk																
NON-MURA	1198	1130	933	720	616	578	204	151	134	102	99	92	90	85	34	7
MURA <= 2.5	770	699	633	485	448	391	363	242	190	75	67	65	62	61	16	2
MURA 5	1649	1584	1407	1124	996	912	477	358	306	165	150	146	141	140	39	8
MURA >= 10	703	672	594	543	517	496	479	458	445	433	429	423	404	393	132	31

Note: DB = double-blind; OL = open-label

Time to Event Analysis: Cox Proportional Hazard Model

A Cox proportional hazards model was utilized to examine the potential for a dose response relationship for CV events on muraglitazar. Subjects were categorized as either having never received muraglitazar (no muraglitazar) or having received ≤ 2.5 mg, 5 mg or ≥ 10 mg of muraglitazar. Subjects never receiving muraglitazar (no muraglitazar) included placebo subjects and subjects randomized to pioglitazone.

Table 8.4.6.1C summarizes the hazard ratios and the 95% confidence intervals for each dose level of muraglitazar relative to the no muraglitazar group. A borderline statistically significant effect was observed for subjects receiving any dose of muraglitazar versus those who did not (p = 0.049). No statistical evidence of trend with respect to muraglitazar dose was observed (p = 0.114). The point estimates of the hazard ratio, while not statistically different, decrease with increasing muraglitazar dose and all three 95% confidence intervals contain 1. One caveat with respect to this analysis is that the subjects on the 10 and 20 mg dose all came from the dose-ranging study in treatment naive subjects, which may have had a lower risk than subjects in the combination studies. Nevertheless, the lack of a dose response is still present between the 2.5 and 5 mg dose.

Table 8.4.6.1C: Hazard Ratios for Muraglitazar versus No Muraglitazar for CV Events, Studies 006, 018 DB + OL, 021, 022, 025: Complete Dataset

Dose of Muraglitazar	Hazard Ratio Estimate	95% Confidence Interval
≤ 2.5 mg	1.6	0.94 to 2.7
5 mg	1.1	0.69 to 1.8
≥ 10mg	0.7	0.39 to 1.29

Note: DB = double-blind; OL = open-label

8.4.6.2 Analysis of Cardiovascular Events: NDA Dataset

Short-Term Data Included in the NDA

During the ST phase of the Phase 2/3 studies, 43 of 2730 subjects had a CV event on muraglitazar (1.5-20 mg dose) while 6 of 823 subjects on pioglitazone and 4 of 528 subjects on placebo had CV events.

The number of subjects with CV events by dose and study are presented in Table 8.4.6.2. This table does not include the 0.5 mg arm of the dose ranging study. There were no CV events on 0.5 mg of muraglitazar.

Table 8.4.6.2: Incidence of CV Events by Dose and Study, Studies 006, 018 DB, 018 OL, 021, 022, 025: Short-Term NDA Dataset

		Placebo	Mura 1.5	Mura 2.5	Mura5	Mura10	Mura 20	Any Pio
006								
	%		0.8%		0.8%	1.2%	1.7%	0.8%
	n/N		2/259		2/245	3/249	4/237	2/251
018DB								
	%	0.9%		1.8%	1.8%			
	n/N	1/115		2/111	2/111			
018OL								
	%				0.9%			
	n/N				1/109			
021								
	%	0%		2.1%	3.6%			
	n/N	0/199		4/191	7/193			
022								
	%	1.4%		2.1%	1.5%			
	n/N	3/214		5/233	3/205			
025								
	%				1.4%			0.7%
	n/N				8/587			4/572
Total %		0.8%	0.8%	2.1%	1.6%	1.2%	1.7%	0.7%
Total n/N		4/528	2/259	11/535	23/1450	3/249	4/237	6/823

Note: This analysis includes 2 subjects from Study 025 with CV events (i.e., CV death) that were not included in the original NDA analysis; DB = double blind, OL = open label.

Overall, the incidence of CV events during the ST phase (monotherapy and combination therapy studies combined) was higher on muraglitazar (2.1% on 2.5 mg and 1.6 % on 5 mg) than on comparators (0.8% on placebo and 0.7% on pioglitazone, any dose). The data integrated from all studies does not suggest a dose response relationship for the incidence of cardiovascular events on muraglitazar. It should be

noted that the incidence data in Table 8.4.6.2 do not correct for differential duration of therapy and are limited to the ST phase of each study. When all of the available data, including the experience from the long-term phase of the studies (i.e., the Complete Dataset) are analyzed using a time to event analysis, there is a similar incidence of CV events for muraglitazar-treated and placebo-treated subjects. However, it should be noted that the Complete Dataset is limited by the fact that it was not designed to definitively assess CV events.

The difference in the incidence of CV events between muraglitazar and placebo is largely caused by an imbalance in these events in a single study (CV168021), in which 11 muraglitazar treated subjects had CV events and none of the placebo-treated subjects had CV events. The absence of CV events in the placebo group in Study CV168021 is disimilar with the placebo groups in the other studies. Excluding Study CV168021 from the analyses of CV events at doses of muraglitazar up to 5 mg resulted in a similar incidence of CV events between muraglitazar and placebo (25 of 1860, 1.3% on muraglitazar and 4 of 329, 1.2% on placebo).

8.4.6.3 Comparison of CV Event Rates in the Muraglitazar Clinical Program with Background Rates Observed in a Longitudinal Diabetic Patient Cohort

Since CV disease is the most important cause of morbidity and mortality in patients with type 2 diabetes, the occurrence of CV events in the muraglitazar program was expected. An analysis was undertaken to compare CV event rates observed in the muraglitazar clinical program with background rates in a longitudinal cohort of patients with diabetes. A cohort of 154,018 patients with diabetes with similar demographic characteristics to those subjects in the muraglitazar clinical program was identified from a managed care organization research database, PharMetrics, and followed for an average of 2.1 years to ascertain the incidence of CV events in this population.

Background incidence rates of cardiac events, defined as unstable angina or myocardial infarction, and cerebrovascular events, defined as stroke or transient ischemic attack, were determined. Only non-fatal events were included in these analyses. Epidemiologic assessment of this cohort showed that the overall non-fatal CV event incidence rate was 19.3 per 1000 patient-years (95% CI: 18.6-20.0).

In order to facilitate a comparison of these background CV event rates with those observed in the muraglitazar clinical program, an additional analysis of the complete muraglitazar dataset was conducted to determine the incidence rate of selected CV events per 1000 patient-years exposure. For this analysis, a CV event was defined as any 1 of the following: CV death, myocardial infarction, acute myocardial infarction, unstable angina, transient ischemic attack, cerebrovascular accident or hemorrhagic stroke. The CV event incidence rate, based on these criteria, for subjects receiving any dose of muraglitazar was 13.6 per 1000 patient-years. This rate suggests that the number of events observed in the muraglitazar clinical program falls within the range observed in a similar population of patients with diabetes.

8.4.6.4 Summary of CV Events

The Kaplan-Meier method indicated a comparable cumulative incidence of CV events for muraglitazar-treated (all doses combined) and placebo-treated subjects. A slight imbalance in the incidence of CV events in muraglitazar-treated subjects, compared to subjects not treated with muraglitazar, was found in a Cox regression analysis of the Complete Dataset. However, there was no evidence for a dose-relationship for CV events in muraglitazar-treated subjects based on both a Cox regression analysis and a Kaplan-Meier analysis. The imbalance noted in the Cox regression analysis is primarily related to data from a single study (CV168021) that was notable for absence of CV events in placebo-treated subjects. Based on review of epidemiologic data, the population in the muraglitazar development program would be expected to have an incidence of CV events comparable to that observed in muraglitazar-treated subjects.

8.4.6.5 Cardiovascular Mortality

There were 9 CV deaths, of 18 total deaths, among muraglitazar-treated subjects. Most (5 of 9) CV deaths occuring in muraglitazar-treated subjects were from a single study (CV168025). One CV death occurred in the placebo group. There were no CV deaths among pioglitazone-treated subjects. It should be noted that all 10 CV deaths were included in the analyses of CV events in prior sections.

The cardiovascular deaths in muraglitazar-treated subjects may be further classified into those due to myocardial infarction, sudden or unwitnessed death, and cerebrovascular accidents as shown in Table 8.4.6.5A.

Table 8.4.6.5A CV Deaths Reported by Dose of Muraglitazar, Studies 006, 018 DB + OL, 021, 022, 025: Complete Dataset

	Muraglitazar Dose (mg)						
	≤ 2.5			5			10 or 20
	Subject Years of Exposure						
	1003			1515			966
Cause	mono	With SU	With Met.	mono	With SU	With Met.	mono
Myocardial Infarction			1		1		1
Sudden or Unwitnessed						4	
Cerebrovascular Accident						2	
Cardiovascular Deaths Total			1		1	6	1

Note: DB = double blind, OL = open label

The 3 events listed as myocardial infarction in Table 8.4.6.5A all had confirmation of this diagnosis including 1 subject who died suddenly but myocardial infarction was found on autopsy. Those subjects listed as sudden or unwitnessed deaths did not have confirmation as to a specific cardiac event. Most sudden or unwitnessed deaths are due to myocardial infarction, pulmonary embolus, or a cardiac electrical event.

The Kaplan-Meier estimates for the cumulative incidence of CV death for muraglitazar-treated subjects is 0.4%, for placebo-treated subjects is 0.6% and zero for pioglitazone treated subjects (see Table 8.4.6.5B).

The number of CV deaths was small, thus statistical conclusions regarding the incidence of CV death are difficult.

Table 8.4.6.5B: Kaplan-Meier Estimate of Cumulative Incidence of CV Death , Studies 006, 018 DB + OL, 021, 022, 025: Complete Dataset

	Any MUR *			Any PIO =<45			Any PLA **		
Time (Month)	Cum. N of Event	N at Risk	Cumulative Incidence (95% CI)	Cum. N of Event	N at Risk	Cumulative Incidence (95% CI)	Cum. N of Event	N at Risk	Cumulative Incidence (95% CI)
0 - 6	5	2969	0.2 (0.0 - 0.4)	0	823	0.0 (0.0 - 0.0)	0	528	0.0 (0.0 - 0.0)
> 6 - 12	9	2369	0.4 (0.1 - 0.7)	0	646	0.0 (0.0 - 0.0)	1	371	0.6 (0.0 - 1.7)
>12 - 18	9	1716	0.4 (0.1 - 0.7)	0	496	0.0 (0.0 - 0.0)	1	114	0.6 (0.0 - 1.7)
>18 - 24	9	944	0.4 (0.1 - 0.7)	0	110	0.0 (0.0 - 0.0)	1	35	0.6 (0.0 - 1.7)
>24 - 30	9	653	0.4 (0.1 - 0.7)	0	96	0.0 (0.0 - 0.0)	1	0	0.6 (0.0 - 1.7)
>30 - 36	9	614	0.4 (0.1 - 0.7)	0	88	0.0 (0.0 - 0.0)	1	0	0.6 (0.0 - 1.7)

Dataset: Treated Subjects
Note: Including all cardiovascular death anytime during study and after the last treatment.
* Includes titration and non-titration data on all doses of muraglitazar during ST + LT Phase for CV168006.
** Non-titrated dose only. For CV168021 and CV168022 ST+LT, subjects who were randomized to placebo and titrated to muraglitazar 2.5 mg in the LT phase will have only data on placebo included.
Note: DB = double blind, OL = open label

From a clinical perspective, it is most informative to review each case individually. Capsule summaries of all CV deaths in the Complete Dataset are provided in the subsequent section. All subjects who had CV death had multiple CV risk factors, in addition to diabetes.

8.4.6.6 Cardiovascular Deaths All Treatment Groups - Complete Dataset Capsule Summaries

Muraglitazar 2.5 mg

- Muraglitazar 2.5 mg/Metformin 2000 mg
  - Subject CV168022-287-1 was a 52-year old Hispanic male with a 4 year history of diabetes and history of hypertension, obesity, hypercholesterolemia, hypertriglyceridemia, mixed dyslipidemia and alcohol use. On study day 10, the subject had the onset of chest pain and sudden death. Postmortem evaluation confirmed a myocardial infarction. The investigator considered the event to be not related to study therapy.

Muraglitazar 5 mg

- Muraglitazar 5 mg/Glyburide 10 mg
  - Subject CV168021-237-5 was a 56-year old Hispanic/Latino female with a 5 year history of diabetes and history of hypertension, unstable angina, obesity, mixed lipidemia, cerebrovascular accident and diabetic retinopathy. On study day 307 she presented to the emergency room with dyspnea, stupor, hyperglycemia and metabolic acidosis. Myocardial infarction was diagnosed and the subject was treated with nitroglycerin, heparin, aspirin, clopidogrel and insulin. On study day 311 heart failure was diagnosed. On study day 312 she required intubation and mechanical ventilation. On study day 320 she developed bradycardia and ventricular fibrillation. She died on study day 321. The investigator considered the events not related to study mediation.
- Muraglitazar 5 mg/Metformin 2000/1500 mg
  - Subject CV168022-153-2 was a 54-year old white male with a 6 year history of diabetes and history of hypertension, obesity (280 lbs.), coronary artery disease, coronary thrombosis and a previous cardiac catheterization. On study day 115 he presented to the emergency room with abdominal bloating, increasing dyspnea, orthopnea and lower extremity edema. And ECG indicated old inferior and extensive anterior infarctions. Heart failure was diagnosed and he was treated with a single dose of furosemide, aspirin, metoprolol and glimepiride. Study medication was discontinued on study day 115. His heart failure rapidly resolved and he had a normal chest x-ray on day

117 and returned to work. He refused further cardiac evaluation. On study day 125, 10 days after the last dose of study medication, he was found dead at this home. The death certificated listed myocardial infarction and occult coronary artery disease as the cause of death. The investigator considered the event as not related to study medication.

- Subject CV168025-193-9 was a 66-year white old female with a 4 year history of diabetes and history of congestive heart failure, hypertension, atrial flutter, transient ischemic attack, microalbuminuria, bilateral lower extremity fluid retention, mitral insufficiency, peripheral vascular disease, overweight and current cigarette use. Her chest x-ray showed cardiomegaly at baseline. During the study (day 164) she was noted to have atrial fibrillation. On several occasions prior to study entry the subject had episodes of shortness of breath and edema that were attributed to incomplete compliance with medications. On study day 201 she attended a party but left early due to shortness of breath and not feeling well. She did not have chest pain. She was later found unresponsive and pronounced dead. The hospital physician stated she had sudden cardiac death probably related to myocardial infarction. The investigator considered the events not related to study medication.
- Subject CV168025-193-10 was a 61- year old white male with a 3 year history of diabetes and history or myocardial infarction, peripheral vascular disease, bilateral lower extremity fluid retention, hypothyroidism, obesity, and cigarette use. His baseline ECG showed left ventricular hypertrophy and an old myocardial infarction. On study day 211 the subject was found dead in bed. It was estimated he had died on study day 208 and had last taken study medication on day 205. The cause of death was not specified. The investigator considered the event not related to study medication.
- Subject CV168025-241-3 was a 67- year old white male with a history of diabetes for 14 years and history of ischemic heart disease, congestive heart failure, hypertension, stable angina, obesity, hypercholesterolemia, hypertriglyceridemia, bilateral lower extremity fluid retention, diabetic neuropathy, diabetic nephropathy and tobacco use. On day 144 the subject died suddenly after someone broke into his home. The death certificate listed the cause of death as chronic ischemic heart disease. Then investigator considered the event not related to study medication.
- Subject CV168025-241-38 was a 60-year old white female with a history of diabetes for 24 years and history of hypertension, obesity, diabetic nephropathy, diabetic neuropathy and diabetic retinopathy. Baseline blood pressure was 164/80 mmHg. On study day 282 the subject was hospitalized for worsening hypertension. On study day 290 the subject had a hemorrhagic stroke from which she died on study day 293. An autopsy confirmed that the

stroke was hemorrhagic. The investigator considered the event not related to study medication.

- Subject CV168025-314-1 was a 53-year old white male with a history of diabetes for 6 years and history of hypertension, stable angina, unstable angina, coronary artery disease, coronary artery bypass graft, hypercholesterolemia and tobacco use. On study day 107 the subject experienced a stroke with right-sided paralysis. The subject died on study day 107. The stroke was not defined as hemorrhagic or non-hemorrhagic. The investigator considered the event not related to the study medication.

Muraglitazar 10 mg

- Subject CV168006-11-8 was a 59- year old white male with a 2 year history of diabetes and a history of hypertension. On study day 49 the subject presented to the emergency room with dyspnea and was diagnosed with myocardial infarction. He did not have chest pain. The cardiac enzymes were elevated. The subject deteriorated and required intubation. On study day 50 a cardiac catheterization was performed which revealed a 99% stenosis of the left main coronary artery and an 80% stenosis of the proximal right coronary artery. An echocardiogram revealed a moderately dilated left ventricle with severe global hypokinesis and an ejection fraction of 15-20%. An intra-aortic balloon pump was placed. On study day 60 life support was withdrawn and the subject died. The investigator considered the event not likely related to study medication.

Placebo/Glyburide 15 mg

- Subject CV168021-33-5 was a 62-year old white male with a history of diabetes for 4 years and history of hypertension, hyperlipidemia, hypertriglyceridemia and obesity. On study day 243 the subject complained of shortness of breath and on day 244 he had sudden death. Autopsy revealed massive pulmonary emboli. The investigator considered the event possibly related to study medication.

8.4.6.7 Discussion

From a clinical perspective, the totality of the data suggests that there is no increased risk of CV events during muraglitazar treatment compared to placebo.

Analyses of atherosclerotic CV events by dose in both the Complete Dataset and the ST NDA dataset did not suggest a dose response relationship for muraglitazar. The absence of a dose response relationship makes it unlikely that atherosclerotic CV events are related to muraglitazar. In contrast, edema and weight gain are related to dose and are thus likely to be associated with muraglitazar (see subsequent discussion).

There is a lack of biologic plausibility in support of a hypothesis that muraglitazar would be associated with an increased incidence of CV events:

- In in vitro and animal studies muraglitazar had multiple effects suggesting a beneficial effect on atherosclerosis and thrombosis including stimulation of cholesterol efflux from macrophages. Furthermore, muraglitazar decreased elevated levels of markers of thrombogenicity in an animal model of diabetes.
- In in-vitro and animal studies as well as a thorough evaluation in humans, showed no potential for muraglitazar to prolong the QT interval at up to high multiples of the clinical exposure at 5 mg.
- Muraglitazar displayed a benign cardiovascular safety profile in routine toxicity studies. There was no evidence of direct cardiotoxicity in animals at any dose level and minimally decreased blood pressure, dose-dependently increased heart weights, and evidence of cardiac hypertrophy only at very high multiples of the human exposure at 5 mg
- In the phase 2 and 3 studies, all evaluated biomarkers of cardiovascular risk: insulin resistance, HDL-C, apo-B as well as markers of inflammation, showed robust beneficial effects with muraglitazar.

The overall clinical profile of muraglitazar therefore supports a hypothesis of a beneficial effect on cardiovascular outcomes. As discussed previously, the number of CV events observed in the muraglitazar clinical program falls within the range observed in a similar population of patients with diabetes.

8.4.7 Heart Failure

All heart failure events from the muraglitazar Phase 2 and 3 studies in subjects with type 2 diabetes occurring during the ST and LT treatment phases are discussed in this section and listed in Attachment 8.4.7. The heart failure reported during the ST treatment of the Phase 2/3 studies (NDA dataset) and an analysis of all reported heart failure events (Complete Dataset) are separately presented. The heart failure data on muraglitazar 10 and 20 mg from Study CV168006 are also presented.

Summary of Results

Overall, heart failure was infrequently reported during treatment with the proposed clinical doses of muraglitazar (2.5 or 5 mg) during the 24-week ST phase of the Phase 2/3

studies. Investigator-identified heart failure was reported for 6 muraglitazar-treated subjects (1 at 2.5 mg; 0.19%, and 5 at 5 mg; 0.34%) and 1 pioglitazone-treated subject (30 mg, 0.17%). For the LT phase, heart failure events were analyzed separately for mono- and combination therapy studies, showing that the risk of heart failure was lowest in mono therapy, and highest in combination with glyburide. The muraglitazar-treated subjects with heart failure had extensive CV histories, and, in some instances, concomitant events that may be responsible for the heart failure. The usual course of heart failure was rapid resolution with diuretic treatment and, usually, with discontinuation of muraglitazar.

Heart failure adjudication: A heart failure adjudication process was in place at the start of the Phase 3 program. The results of this adjudication process for the NDA Dataset are included in this document. The heart failure adjudication process indicated that, in addition to subjects identified by the investigator as having heart failure, a small proportion of subjects with edema of moderate or higher intensity or with dyspnea appeared to have heart failure. 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. See Section 8.4.7.2 for more details on the Adjudication Committee.

Detailed results on heart failure are presented below.

8.4.7.1 Investigator-Reported Adverse Events of Heart Failure

Short-term: Muraglitazar up to 5 mg (NDA Dataset)

Heart failure was reported for 6 subjects who received muraglitazar (1 at 2.5 mg; 0.19%, and 5 at 5 mg; 0.34%) and 1 subject who received pioglitazone 30 mg (0.17%) therapy for 24 weeks. The incidence of heart failure when calculated per 1000 patient years of exposure was 4.5 events for the 2.5 mg dose, 8.3 events for 5 mg and 4.2 events for pioglitazone 30 mg (Table 8.4.7.1A). There were no cases of investigator-reported heart failure in the monotherapy studies.

- Two subjects treated with muraglitazar (1 at 2.5 mg and 1 at 5 mg) in combination with sulfonylurea had heart failure events; the event was considered a SAE in 1 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 a SAE in 3 cases. The study drug was discontinued in 3 subjects.
- One subject (CV168025-337-5) treated with pioglitazone (30 mg) in combination with metformin had a heart failure event; the event was not considered a SAE but the study drug was discontinued.
- Heart failure was not reported for subjects randomized to placebo treatment.

The 6 subjects who experienced heart failure in the muraglitazar combination therapy groups had extensive histories of CV disease (including history of heart failure in 2 subjects) and, in some instances, intercurrent events that may be responsible for their heart failure:

- Subject CV168021-69-1: diabetes for 6 years, MI, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and lower extremity edema. In addition to these historical events of interest, the following other events occurring around the time of reported heart failure were also noted: 1) heart block with ventricular rates in the 30s and 40s, and 2) this subject's heart failure resolved with placement of a pacemaker. The investigator indicated that the heart failure was not related to the study drug treatment.
- Subject CV168021-301-5: diabetes for 10 years, hypertension for 30 years, mixed dyslipidemia, atrial fibrillation, obesity, and NYHA Class II, cardiomegaly on chest x-ray. In addition to these historical events of interest, the following other events occurring around the time of reported heart failure were also noted: 1) an increase in atenolol to 40 mg 3 times a day for treatment of atrial fibrillation prior to heart failure onset, and 2) discontinuation of atenolol and furosemide treatment resulted in resolution of heart failure symptoms in 4 days. The investigator indicated that the heart failure was possibly related to the study drug treatment.
- Subject CV168022-153-2: diabetes for 6 years and hypertension for 10 years. The investigator indicated that the heart failure was probably related to the study drug treatment.
- Subject CV168025-45-5: diabetes for 3 years, hypertension for 24 years, heart failure, MI, carotid artery disease, overweight, hypercholesterolemia, lower extremity pitting edema, and diabetic nephropathy. The investigator indicated that the heart failure was possibly related to the study drug treatment.
- Subject CV168025-48-6: diabetes for 5 years, hypertension, obesity, and bilateral lower extremity edema. In addition to these historical events of interest, the following other events occurring around the time of reported heart failure were also noted: 1) diagnosed as having worsening malignant hypertension at the time of heart failure diagnosis, 2) treated with clonidine, enalapril, furosemide, and hydralazine and 3) discontinued from labetalol with discharge 4 days after hospital admission. The

investigator indicated that the heart failure was not related to the study drug treatment.

- Subject CV168025-236-7: diabetes for 8 years, hypertension for 14 years, MI, stable angina, peripheral vascular disease for 14 years, diabetic neuropathy for 5 years, obesity, and aortic stenosis. The investigator indicated that the heart failure was not likely related to the study drug treatment.

Five of the 6 subjects diagnosed with heart failure were treated with furosemide with resolution or improvement of heart failure signs and symptoms 2, 4, 11, 15, and 16 days after diagnosis, respectively. One of these 5 subjects (CV168022-153-2) had rapid resolution of heart failure and a normal chest x-ray 2 days after discontinuing muraglitazar and receiving a single 40 mg dose of intravenous furosemide. However, the subject died of MI 9 days after study drug was discontinued. He had refused further follow-up prior to this event. The sixth subject (CV168021-69-1) diagnosed with heart failure received a pacemaker and did not receive furosemide.

LT Muraglitazar up to 5 mg

Heart failure was reported during LT muraglitazar therapy for 3 subjects treated with muraglitazar 2.5 mg and 7 subjects treated with 5 mg. One additional subject receiving pioglitazone 30 mg also had heart failure during LT treatment.

Muraglitazar 2.5 mg

Of the subjects receiving muraglitazar 2.5 mg who developed heart failure during LT therapy, 2 were receiving concomitant therapy with sulfonylurea (Study CV168021) and 1 concomitant therapy with metformin (Study CV168022).

- Subject CV168021-55-2 had a SAE (preferred term cardiac failure congestive, severe intensity, possibly related, study drug discontinued) after 410 days muraglitazar therapy. The subject presented to the emergency room with shortness of breath and chest pain/pressure and was diagnosed with myocardial infarction and heart failure. The subject had a cardiac catheterization and coronary artery bypass graft surgery and continued to have heart failure when last seen. Relevant history included hypertension and diabetic nephropathy.
- Subject CV168021-209-10 had an AE (preferred term cardiac failure congestive, moderate intensity, unrelated, study drug discontinued) after 358 days muraglitazar therapy. The subject presented to the physicians office with retrosternal chest pain, dyspnea on exertion and moderate edema. The chest x-ray was normal and the

ejection fraction was 73%. The subject was treated with furosemide and nitrates. The heart failure had not resolved at the last visit. History included hypertension, diabetic neuropathy and left ventricular hypertrophy on the ECG.

- Subject CV168022-255-11 had an AE (preferred term cardiac failure, severe intensity, possibly related, study drug discontinued) after 192 days muraglitazar therapy. The subject presented with dyspnea and fatigue. Rales and edema were present and the x-ray revealed cardiomegaly. Treatment with furosemide resulted in resolution the heart failure in 2 days. History included hypertension, coronary artery disease and myocardial infarction.

Muraglitazar 5 mg

Of the subjects receiving muraglitazar 5 mg who developed heart failure, 3 were receiving monotherapy (Study CV168006), 2 were receiving concomitant sulfonylurea (Study CV168021) and 2 were receiving concomitant metformin (Study CV168025).

- Subject CV168006-085-1 had an AE (preferred term cardiac failure congestive, moderate intensity, possibly related, study drug discontinued) after 375 days muraglitazar treatment. The subject presented with a 15 day history of shortness of breath and had a chest x-ray consistent with heart failure. The subject had normal left ventricular function. Treatment was with furosemide and heart failure was still present at the last visit. History included hypertension, obesity and chest pain.
- Subject CV168006-245-27 had a SAE (preferred term cardiac failure congestive, severe intensity, possibly related, study drug discontinued) after 924 days of muraglitazar treatment. The subject presented with a 4 day history of dyspnea, orthopnea, paroxysmal nocturnal dyspnea and cough. The chest x-ray showed severe pulmonary edema and cardiomegaly. The ejection fraction was 41%. The subject was treated with furosemide and the heart failure resolved in 1 day. History included hypertension, stable angina, obesity and cardiomegaly.
- Subject CV168006-419-47 had a SAE (preferred term pulmonary edema, severe intensity, possibly related, study drug discontinued) after 356 days of muraglitazar therapy. The subject awoke with severe shortness of breath and went to the emergency room where rales and slight edema were observed. The subject was treated with furosemide and nitrates with resolution in 2 days. There was a history of hypertension.
- Subject CV168021-237-5 had a SAE (preferred term cardiac failure acute, very severe intensity, unrelated to study drug) after 311 days of muraglitazar treatment. The subject was diagnosed with acute myocardial infarction 4 days prior to the onset of heart failure. The subject was treated with multiple medications including furosemide and dobutamine but developed ventricular fibrillation and died 14 days

after the myocardial infarction and 10 days after the onset of heart failure. The history included hypertension, unstable angina, obesity and a cerebrovascular accident.

- Subject CV168021-244-14 had a SAE (preferred term cardiac failure congestive, severe intensity, possibly related, study drug discontinued) after 429 days of muraglitazar treatment. The subject presented with atrial fibrillation and heart failure. The ejection fraction was 67%. The subject was treated with bisoprolol and the event resolved in 35 days. History included hypertension, obesity and increased lung vascularization on chest x-ray.
- Subject CV168025-193-9 had a SAE (preferred term cardiac failure, very serve intensity, unrelated to study drug) after 210 days of muraglitazar treatment. The subject developed shortness of breath and went to bed. She was later found dead in the bathroom by her husband. They physician described the event as sudden cardiac death probably related to a myocardial infarction. The medical history included congestive heart failure, hypertension, peripheral vascular disease, transient ischemic attack, edema, atrial flutter, mitral insufficiency, chronic obstructive pulmonary disease and microalbuminiria.
- Subject CV168025-235-3 had a SAE (preferred term cardiac failure congestive, moderate intensity, possibly related, study drug discontinued) after 262 days of muraglitazar therapy. The subject presented with 3 week history of exertional dyspnea and peripheral edema. The chest x-ray showed cardiomegaly and the echocardiogram was read as left ventricular hypertrophy and diastolic dysfunction with an ejection fraction of 57%. The subject was treated with furosemide and an ACE inhibitor and the heart failure resolved in 6 days. The history included hypertension, coronary artery disease, stable angina and cardiac dilation.

An additional subject (CV168006-41-2), who was treated with muraglitazar 5 mg, had a non-serious adverse event of heart failure 1 day after discontinuing study medication. Due to the counting rules employed in the program, this non-serious event occurring after discontinuation of study medication is not counted in the table describing the incidence of heart failure.

The LT cases of heart failure are consistent with what has been described in the ST subjects. A significant history of cardiovascular disease is frequently noted and the clinicians caring for these subjects most often discontinue muraglitazar therapy and initiate standard therapy (including diuretics) for heart failure upon diagnosis.

Table 8.4.7.1B shows the number of subjects with investigator-reported heart failure per 1000 years of exposure for muraglitazar 2.5 mg, muraglitazar 5 mg, placebo, and pioglitazone 30 mg in the Complete Dataset. The incidence of investigator-reported heart

failure for muraglitazar 5 mg and pioglitazone 30 mg are similar to what was reported in the NDA database. No heart failure has been reported by investigators in subjects receiving placebo. The incidence for muraglitazar 2.5 mg in the Complete Dataset is similar to muraglitazar 5 mg due to 3 additional events in the Complete Dataset.

Table 8.4.7.1A: Incidence Rates and Number of Subjects with All Reported Heart Failure Event(s) Per 1000 Years of Exposure, All Subjects in Phase 3 Studies and Short-Term of CV168006

		MUR 2.5	MUR 5	PLA	PIO 30
CV168018	# Subj. with Event	0	0	0	
	Years of Exposure	46.60	87.03	43.84	
	Subjects/1000 Years	0	0	0	
CV168021	# Subj. with Event	1	1	0	
	Years of Exposure	79.04	83.53	77.91	
	Subjects/1000 Years	12.7	12.0	0	
CV168022	# Subj. with Event	0	1	0	
	Years of Exposure	98.28	87.27	82.43	
	Subjects/1000 Years	0	11.5	0	
CV168025	# Subj. with Event		3		1
	Years of Exposure		251.22		239.71
	Subjects/1000 Years		11.9		4.2
CV168006 ST	# Subj. with Event		0		
	Years of Exposure		92.05		
	Subjects/1000 Years		0		
Total	# Subj. with Event	1	5	0	1
	Years of Exposure	223.92	601.10	204.18	239.71
	Subjects/1000 Years	4.5	8.3	0	4.2

Dataset: Treated Subjects and Open-Label Cohort MedDRA Version: 7.0
Includes all CHF-related terms based upon the muraglitazar predefined list of events.
Non-serious events up to the last treatment date of Short-Term Phase included.
Serious events up to 30 days post Short-Term Phase (but prior to Long-Term Phase) included.
Includes CV168006 Mur 5 mg arm ST Phase up to rescue medication, CV168018 including OL cohort, CV168021, CV168022 and CV168025.
Years of exposure is the duration of treatment up to the date of the first CHF event, if applicable

Table 8.4.7.1B: Incidence of All Investigator-Reported Heart Failure Event(s) Per 1000 Years of Exposure CV168006 ST+LT, 018 DB+OL, 021 ST+LT, 022 ST+LT, and 025 ST+LT

		MUR 2.5	MUR 5	PLA	PIO 30
CV168018 DB+OL	# of Subjects with at Least One Event	0	0	0	
	Years of Exposure	46.60	87.03	43.84	
	Subjects/1000 Years	0	0	0	
CV168021 ST+LT	# of Subjects with at Least One Event	3	3	0	
	Years of Exposure	206.45	206.68	123.82	
	Subjects/1000 Years	14.53	14.51	0	
CV168022 ST+LT	# of Subjects with at Least One Event	1	1	0	
	Years of Exposure	263.48	239.23	164.49	
	Subjects/1000 Years	3.80	4.18	0	
CV168025 ST+LT	# of Subjects with at Least One Event		5		2
	Years of Exposure		468.70		439.83
	Subjects/1000 Years		10.67		4.55
CV168006 ST+LT	# of Subjects with at Least One Event		3		
	Years of Exposure		517.05		
	Subjects/1000 Years		5.80		
Total	# of Subjects with at Least One Event	4	12	0	2
	Years of Exposure	516.53	1518.69	332.15	439.83
	Subjects/1000 Years	7.74	7.90	0	4.55

Dataset: Treated Subjects and Open-Label Cohort MedDRA Version: 8.0
Includes all CHF-related terms based upon the muraglitazar predefined list of events.
Non-serious events up 1 day post last treatment day included.
Serious events up to 30 days post last treatment day included.
Years of exposure is the duration of treatment up to the date of the first CHF event, if applicable

Subjects Receiving Muraglitazar 10 mg or 20 mg during short- and long-term treatment in the dose ranging study

In Study CV168006, 6 subjects receiving muraglitazar 10 mg and 6 subjects receiving muraglitazar 20 mg were reported to have heart failure during the ST or LT Phase (Attachment 8.4.7.1). Heart failure was reported as a SAE in 5 of these 12 subjects. The study drug was discontinued in 8 subjects. Heart failure events were reported as continuing at last observation in 2 of the subjects, and as having resolved in 10 subjects.

Conclusions: Investigator Identified Heart Failure

Overall, the small number of heart failure events precludes drawing conclusions regarding definitive heart failure incidence rates from the data in the muraglitazar clinical program. Heart failure occurred more frequently during dosing with 5 mg muraglitazar than with 2.5 mg, which would be consistent with a larger PPARγ agonist effect being associated with both greater antihyperglycemic efficacy and a greater incidence of heart failure. This was also observed in the dose-ranging Study CV168006. In addition, the heart failure incidence was lowest in monotherapy, and highest in combination with glyburide.

The number of subjects with at least 1 event per 1000 patient years of exposure is similar when the LT data are included. These LT data indicate that heart failure is unlikely to be a delayed event for which the incidence increases disproportionately over time.

The expected risk of heart failure in subjects with type 2 diabetes is critically dependent on age and other risk factors. A recent study of heart failure in a population of > 48,000 subjects with diabetes (mean age: 58 years) found incidence rates of hospitalization for heart failure of 4.5 to 9.2 events per 1000 person years.[39] Another study of all heart failure (including those not hospitalized) in a population of 8460 diabetic subjects (mean age: 63 years) found an incidence of 30.9 events per 1000 person years.[40] Although these data cannot be directly compared with the observed incidence from controlled clinical trials in the muraglitazar program, it does indicate that heart failure is an expected event in subjects with type 2 diabetes.

In addition, as the need for more glycemic efficacy arises, the risk of heart failure will increase regardless whether the dose of a PPARγ agonist is increased or other therapies are added. For instance in a 26-week study with rosiglitazone in combination with insulin, the incidence of heart failure in the insulin alone arm was 1%, 2% on insulin plus rosiglitazone 4 mg, and 3% on insulin plus rosiglitazone 8 mg.[41]

8.4.7.2 Heart Failure Adjudication

The diagnosis of heart failure in subjects with type 2 diabetes treated with PPARγ agonist therapy may be especially difficult because edema and weight gain unrelated to heart failure may occur with this therapy. Heart failure may be over-diagnosed due to the presence of edema and investigator belief that PPARγ agonism may be associated with heart failure. Alternatively, heart failure may be under-diagnosed if edema or other signs and symptoms are routinely considered to be benign drug effects unrelated to heart failure. Moreover, heart failure may be due to intercurrent events (such as MI or arrhythmia), which are unrelated to PPARγ therapy. To ensure that all possible episodes of heart failure were identified and fully characterized, a heart failure adjudication process was developed for the Phase 3 muraglitazar clinical program. The committee had access to some information (eg, NT-proBNP values) which was not available to the investigators.

The Adjudication Committee comprised 3 independent cardiologists (not affiliated with the Sponsors) experienced in performing heart failure adjudication. Candidate events for adjudication were identified via a predefined list of MedDRA Preferred Terms (PTs) that could possibly represent heart failure (Attachment 8.4.7.2). These terms included those of heart failure or related terms, which were all adjudicated irrespective of intensity, as well as those of edema and related terms that were adjudicated if they were of moderate or greater intensity. The Committee was charged with determining if the event was or was not an event of heart failure. In those instances where heart failure was present, the Committee determined if the heart failure was due to an intercurrent event, and if the heart failure was likely present prior to study treatment. Investigators, committee members, and the Sponsors were all blinded to the treatment assignments associated with the events under review.

Muraglitazar-treated Subjects

Adjudication of Investigator-identified Heart Failure Events in Phase 3 Studies

The Adjudication Committee confirmed that heart failure was present in each of the 6 muraglitazar-treated subjects (2.5 or 5 mg) identified by the investigators as having heart failure in the muraglitazar combination studies. The heart failure for these 6 subjects was described by the Committee as follows:

- 4 due to an intercurrent event (heart block/bradycardia; adjustment of beta-blocker; accelerated hypertension; and aortic stenosis).
- 2 not due to an intercurrent event. (One of these 2 subjects was hospitalized, both were discontinued from the study therapy, and both were treated with diuretics. The heart failure events resolved 2 and 7 days after onset).

One of these 2 subjects was believed by the Committee to likely have had heart failure at baseline.

Adjudication of Events that were not identified as Heart Failure by the Investigator in Phase 3 Studies

The Adjudication Committee indicated that heart failure was present in 7 muraglitazar-treated subjects who were not identified by the investigators as having heart failure:

- A total of 31 events of edema or related terms of ≥ moderate intensity were reported by the investigators; 5 of these 29 events (in 5 subjects) were adjudicated to be heart failure.
    - The PTs for the investigator-identified events for these 5 adjudicated cases were ‘edema peripheral’ (4 subjects) and ‘generalized edema’ (1 subject).
    - Four of these 5 subjects were treated with diuretics or by an increased dose of diuretic.
    - Study drug was discontinued in 1 subject.
    - The AE of edema resolved in 13, 22, 28, 39, and 86 days.
- For dyspnea or dyspnea exertional, 11 events (in 11 subjects) of any intensity were reported; 2 of these 11 events (in 2 subjects) were adjudicated to be heart failure. The PT for the investigator-identified events for these 2 adjudicated cases was ‘dyspnea.’ One of these 2 subjects was not treated, and the other was treated with diuretics. The AEs of dyspnea resolved after 20 and 3 days.

Heart failure for these 7 subjects was described by the Adjudication Committee as follows:

- Due to an intercurrent event in 3 of 7 subjects (calcium channel blocker treatment, cessation of diuretic, and worsening renal failure in 1; hypertension and upper respiratory infection in 1; and atrial fibrillation in 1).
- Not due to intercurrent event in 4 of 7 subjects. None of these subjects was hospitalized.
- The Committee stated that 2 subjects were likely to have heart failure at baseline.

Pioglitazone-treated subjects

One pioglitazone-treated subject identified by the investigator as having heart failure was considered by the Adjudication Committee not to have heart failure. The Committee noted that another pioglitazone-treated subject, with investigator-identified peripheral edema, had heart failure. This heart failure was not due to an intercurrent event and was described as unlikely to have been present prior to the pioglitazone treatment

Conclusions from Heart Failure Adjudication of Phase 3 Studies

Based on the opinions of the heart failure Adjudication Committee, the following observations may be made:

- Events identified by the investigator as heart failure were usually adjudicated as heart failure, indicating that over-diagnosis of heart failure was not a common phenomenon. This allays concern that knowledge of possible heart failure and the presence of edema with PPARγ agonism may result in over-diagnosis of heart failure.
- Edema of moderate or greater intensity and dyspnea of any intensity were adjudicated to be heart failure in a small percentage of cases. The heart failure identified in these subjects appeared not to be severe; no subjects were hospitalized and study therapy was continued in most cases. These subjects were usually treated with diuretics (as were subjects with investigator-identified heart failure) with resolution of the event in each instance, indicating that failure to identify these events as heart failure had little effect on subject treatment or outcome.
- 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 such as arrhythmia, accelerated hypertension, or a change in concomitant medications. However, it is likely that the fluid retention caused by muraglitazar may have contributed to the symptoms of heart failure in these subjects.

8.4.8 Risk Factors for the Development of Heart Failure in the Muraglitazar Program

8.4.8.1 Specific Disease History

A consensus statement from the American Heart Association and the American Diabetes Association lists risk factors for heart failure in subjects treated with TZDs[42]. These risk factors include a history of heart failure, a history of prior myocardial infarction or symptomatic coronary artery disease, hypertension, and preexisting edema. The data from the Specific Disease History pages of the case report forms used in the muraglitazar Phase 3 program in the treatment of diabetes have been reviewed to determine if risk factors described in the consensus statement identified subjects at increased risk of heart failure during muraglitazar treatment.

The Specific Disease History pages of the case report form asked if the subject had a history of a number of medical conditions. The yes/no responses to a history of congestive heart failure, hypertension, and bilateral lower extremity fluid retention were each tallied separately. There were a number of questions which could all be considered manifestations of atherosclerotic disease and the subject was considered to have atherosclerotic disease if the answer to any of these questions was yes. The specific questions which were grouped as atherosclerotic disease are a history of myocardial infarction, hospitalization for unstable angina, stable angina, percutaneous coronary intervention, coronary artery bypass graft, carotid artery disease, carotid endarterectomy or stenting, peripheral vascular disease, peripheral vascular surgery, coronary artery disease, cerebrovascular accident and transient ischemic attack.

For each of these 4 historical questions (congestive heart failure, hypertension, bilateral lower extremity fluid retention, and atherosclerotic disease), the incidence of adjudicated heart failure for those subjects with the history and for those without the history was determined. No statistical testing was performed.

The results are shown in Table 8.4.8.1. Of the 24 subjects with a history of congestive heart failure, 2 (8.3%) had an episode of heart failure while receiving muraglitazar. A history of hypertension was present in 55.8% of muraglitazar-treated Phase 3 subjects and 1.0% of these subjects had adjudicated heart failure as compared to 0.4% of those

without hypertension. Heart failure was more frequent (2.9%) in subjects with a history of bilateral lower extremity fluid retention than in those without this history (0.5%). A history of atherosclerotic heart disease was present in 12.9% of subjects. Heart failure occurred in 4.0% of subjects with this history as compared to 0.3% in those without this history.

These results in muraglitazar-treated subjects are consistent with the risk factors for heart failure with TZD treatment which have been identified in the consensus statement. The results provide some estimate of what the increase in heart failure risk is for the examined items although the small number of heart failure episodes limits the reliability of these conclusions.

Table 8.4.8.1: Incidence of Heart Failure by Risk Factors

History	Subjects with History n/N (%)	Subjects without History n/N (%)
Hypertension	10/973 (1.0%)	3/770 (0.4%)
Atherosclerotic Disease	9/225 (4.0%)	4/1518 (0.3%)
Bilateral Lower Extremity Fluid Retention	6/208 (2.9%)	7/1535 (0.5%)
Congestive Heart Failure	2/24 (8.3%)	11/1719 (0.6%)
Beta-blocker Use During Study	7/227 (3.1%)	6/1516 (0.4%)

8.4.8.2 Concomitant Beta-Blocker Treatment

Many of the subjects who developed heart failure were receiving concomitant treatment with beta-blockers. Although beta-blocker therapy has been prohibited in some studies of antidiabetic therapies, this treatment was allowed in the muraglitazar program and 13% of the muraglitazar-treated subjects in Phase 3 received beta-blocker therapy at some time during the study (excluding ophthalmologic beta-blocker use, but including amiodarone which blocks the beta-adrenergic receptor).

The incidence of adjudicated heart failure for muraglitazar-treated subjects who did or did not receive beta-blocker treatment during study is shown in Table 8.4.8.1. Of 227 subjects who received beta-blocker treatment at any time during study, 7 (3.1%) had an

episode of heart failure while taking a beta blocker as compared to 6/1516 (0.4%) of subjects who did not receive beta-blocker.

Most likely, beta-blocker treatment is a marker identifying patients at risk for heart failure. Beta-blocker treatment is frequently prescribed in circumstances (eg, post myocardial infarction) in which the risk of heart failure is increased. Among the 13 muraglitazar-treated subjects in the Phase 3 program who were adjudicated to have heart failure there was considerable overlap among those with a history of atherosclerotic disease and those who were treated with beta-blockers; 5 with both, 3 with a history of atherosclerotic disease only, 2 with beta-blocker use only. It is possible that in addition to being a marker of patients with underlying heart disease that beta-blocker use may independently be associated with the risk of heart failure. A recent publication, evaluating the use of TZDs and risk of heart failure in type 2 diabetes, examined a health insurance claims database which included 5441 TZD-treated patients and 28,103 patients treated with other oral antihyperglycemic agents.[43] In addition to finding that TZD use increased the risk of heart failure, beta-blocker use was associated with a univariate hazard ratio for heart failure of 1.83 ($p < 0.001$) and a multivariate hazard ratio of 1.35 ($p = 0.021$).

8.4.8.3 Summary

The small number of subjects with heart failure in the muraglitazar program limits our ability to identity risk factors for heart failure associated with muraglitazar treatment. The results of the analyses of specific disease histories are consistent with the risk factors for heart failure with TZD treatment which have been identified in the AHD/ADA consensus statement. Our beta-blocker findings are consistent with beta-blocker use as a marker for patients at risk for heart failure.

8.5 Special Safety Considerations

8.5.1 Edema-related Adverse Events

Edema is a well recognized side effect of PPARγ agonists. Although its etiology is not well known it is thought to be secondary to the vasodilation and fluid retention observed with PPARγ agonists. Recent data has been published that suggests the role of PPARγ agonist receptors located in the collecting duct of the kidney as a possible mechanism for

the fluid retention associated with PPARγ agonists.[28,44] This appears to result in an increase in sodium and water reabsorption which can then result in the clinical manifestation of edema.

Across the muraglitazar clinical program events of edema were carefully captured. For all studies investigators were required to assess the presence or absence of bilateral pitting edema at baseline. For the dose ranging study, investigators were also required to assess the presence of bilateral pitting edema at each study visit. During the Phase 3 program edema was captured by standard safety assessments.

The incidence of baseline pitting edema ranged from 3.7 to 11.4%, indicating that edema is a relatively frequent condition in this patient population. During treatment, the incidence of edema-related AEs was higher for muraglitazar than for placebo when administered as mono-, or combination therapy. It is important to note the relatively high incidence rate of edema for the placebo group (3.7% to 7.8%).

In summary, 1) the incidence of edema-related AEs was dose-related, 2) the majority of the events were mild in intensity, and 3) few subjects were discontinued due to edema.

The data for edema-related AEs are presented below for monotherapy and combination therapy.

Monotherapy

Dose-Ranging Study CV168006

The number of subjects who reported edema-related AEs during the ST phase for pioglitazone 15 mg was 14.3%, and for muraglitazar 1.5 mg and 5 mg was 9.7% and 8.6%, respectively (Table 8.5.1A). All of the edema-related AEs were mild or moderate in intensity. None of the muraglitazar-treated subjects, at doses up to 5 mg, discontinued study treatment due to edema-related AEs during the ST phase.

Phase 3 Monotherapy Study CV168018

The number of subjects who reported edema-related AEs during the ST phase was 8.1% on muraglitazar 2.5 mg, 11.4% on muraglitazar 5 mg, and 7.8% on placebo

(Table 8.5.1A). All of the edema-related AEs were mild or moderate in intensity. Two subjects discontinued study treatment for edema-related AEs (both in the placebo group).

Combination Therapy with Sulfonylurea

The incidence of edema-related AEs during the ST phase was higher when muraglitazar (2.5 or 5 mg) was administered in combination with sulfonylurea (9.4% and 9.8%, respectively) versus combination of placebo with sulfonylurea (7.0%) (Table 8.5.1A). All of the edema-related AEs were mild or moderate in intensity. Two subjects discontinued study treatment during the ST phase due to edema-related AEs: 1 on muraglitazar 2.5 mg and 1 on muraglitazar 5 mg.

Combination Therapy with Metformin

The incidence of edema-related AEs was higher for muraglitazar than for placebo or pioglitazone during the ST phase of the combination with metformin studies (Table 8.5.1A).

In study CV168022 the placebo group had a lower rate than observed in the other studies (3.7% vs 7.0% in the monotherapy study and 7.0% in the glyburide combination study). The reason for this lower rate is not known. The incidence of edema-related AEs for muraglitazar 5 mg in combination with metformin was higher in Study CV168022 (15.6%) than in Study CV168025 (9.2%) in the same patient population. The rate reported for muraglitazar 5 mg in Study CV168025 was in the range observed across monotherapy and combination with glyburide studies (8.6% to 11.4%).

The majority of edema-related AEs on muraglitazar were mild in intensity; there were 3 cases of severe edema-related AEs (2 on muraglitazar 5 mg and 1 on pioglitazone) (Table 8.5.1A).

A total of 3 subjects discontinued due to edema-related AEs: two on muraglitazar 5 mg were mild in severity and 1 was severe. One subject discontinued due to severe edema on pioglitazone 30 mg.

Table 8.5.1A: Number (%) of Subjects who Reported Edema-related AEs by Intensity, ST phase

	Placebo	Mura 1.5 mg	Mura 2.5 mg	Mura 5 mg	Pioglitazone
Dose-Ranging (CV168006ST)	--	**N = 259**	--	**N = 245**	**N = 251**[a]
Total	--	25 (9.7)	--	21 (8.6)	36 (14.3)
Mild	--	20 (7.7)	--	18 (7.3)	33 (13.1)
Moderate	--	5 (1.9)	--	3 (1.2)	3 (1.2)
Monotherapy (CV168018)	**N = 115**	--	**N = 111**	**N = 114**	--
Total	9 (7.8)	--	9 (8.1)	13 (11.4)	--
Mild	7 (6.1)	--	7 (6.3)	12 (10.5)	--
Moderate	2 (1.7)	--	2 (1.8)	1 (0.9)	--
Combination with Glyburide (CV168021)	**N = 199**	--	**N = 191**	**N = 193**	--
Total	14 (7.0)	--	18 (9.4)	19 (9.8)	--
Mild	13 (6.5)	--	14 (7.3)	16 (8.3)	--
Moderate	1 (0.5)	--	4 (2.1)	3 (1.6)	--
Combination with Metformin (CV168022)	**N = 214**	--	**N =233**	**N = 205**	--
Total	8 (3.7)	--	22 (9.4)	32 (15.6)	--
Mild	6 (2.8)	--	17 (7.3)	27 (13.2)	--
Moderate	2 (0.9)	--	5 (2.1)	5 (2.4)	--
TZD Comparator (CV168025)	--	--	--	**N = 587**	**N = 572**[b]
Total	--	--	--	54 (9.2)	41 (7.2)
Mild	--	--	--	46 (7.8)	37 (6.5)
Moderate	--	--	--	7 (1.2)	3 (0.5)
Severe	--	--	--	1 (0.2)	1 (0.2)

[a] Pioglitazone 15 mg

[b] Pioglitazone 30 mg

Monotherapy Long-term treatment (CV168006)

As expected the incidence of edema during the LT phase of the study for the muraglitazar 5 mg and under and pioglitazone was higher than during the ST phase. However, there were fewer new or worsening events of edema after the initial 24 weeks of the ST phase. Overall, the severity of edema for the majority of subjects was mild or moderate and few subjects were discontinued due to edema during the LT phase.

Subgroup Analysis on Edema-related Events

Within the muraglitazar group, the incidence of edema-related events was, 1) similar in non-elderly vs elderly (9.9% versus 11.0%), 2) higher in females relative to males (11.7% versus 8.7%), and 3) higher in Blacks relative to Whites (14.5% versus 10.0%). However, the incidence was also higher in females vs males and Blacks vs Whites for the placebo and pioglitazone groups.

In the muraglitazar treatment group, the incidence of edema-related events was higher in 1) subjects with BMI ≥ 30 relative to < 30 (13.2% and 6.2%, respectively), and 2) subjects with a baseline fasting insulin level ≥ 12 μU/mL relative to < 12 μU/mL (12.0% and 8.0%, respectively). This pattern was also seen for the pioglitazone group but not for the placebo group.

8.5.2 Change from Baseline in Body Weight (NDA Dataset)

Weight gain is associated with several anti-diabetic treatments: insulin, sulphonylureas, and PPARγ agonists. As expected based on the PPARγ experience, a dose-related increase in body weight was observed when muraglitazar was administered as monotherapy or combination therapy. The increase in weight was within the range reported for PPARγ agonists and was related to the therapeutic response, as those individuals who gained more weight, also had a greater degree of A1C lowering. The data for body weight are presented for monotherapy (ST and LT phases) as well as for combination therapy.

Weight gain in monotherapy

Mean weight gain after 24 weeks of treatment was higher with muraglitazar 5 mg than with either pioglitazone 15 mg, muraglitazar 2.5 mg, or placebo (Table 8.5.2A). The mean weight gain was comparable for muraglitazar 1.5 mg and pioglitazone 15 mg.

The mean weight gain on muraglitazar 5 mg was higher for the OL cohort (4.2 kg) relative to the double-blind cohort (2.1 kg) in Study CV168018. Subjects in the OL cohort had poorer glycemic control at screening (A1C > 10 to ≤ 12%) than those who were randomized, had a greater therapeutic response and would be expected to have a greater reduction in glycosuria than the randomized subjects. This may result in a greater weight gain for the OL group than that for the randomized group.

During 104 weeks of treatment subjects continued to gain weight: for muraglitazar 5 mg (non-titrated group) the mean change from baseline in weight was 5.9 kg. However, this same group was also able to maintain an A1C level of 6.5% at the end of the 104 week treatment period.

Weight Gain in Combination with Sulfonylurea and Metformin

Compared to placebo, the weight gain at Week 24 was higher when muraglitazar (2.5 or 5 mg) was administered in combination with either a sulfonylurea or metformin (Table 8.5.2A). As expected, weight gain also seemed to be higher when muraglitazar was added to glyburide than when added to metformin.

Table 8.5.2A: Mean Change from Baseline at Week 24 in Body Weight (kg) (ST Phase)

Study	Treatment	n	Baseline Mean (SD)	Week 24 Mean (SD)	Change from Baseline Mean (SE)
Monotherapy					
CV168006 *	MUR 1.5	140	87.81 (15.64)	87.68 (16.10)	-0.13 (0.30)
	MUR 5	168	89.76 (15.42)	91.74 (16.80)	1.98 (0.31)
	PIO 15	135	91.84 (15.54)	92.26 (16.17)	0.43 (0.33)
CV168018	MUR 2.5	91	89.12 (18.67)	90.26 (18.95)	1.14 (0.41)
	MUR 5	92	88.55 (20.62)	90.65 (21.33)	2.10 (0.40)
	PLA	74	85.26 (20.80)	84.52 (20.96)	-0.74 (0.41)
All	MUR 5	260	89.33 (17.41)	91.36 (18.50)	2.03 (0.24)
CV168018	MUR 5 OL	62	84.42 (17.06)	88.57 (17.28)	4.15 (0.51)
Combination with SU					
CV168021	MUR 2.5+GLY	157	82.45 (18.28)	85.17 (18.13)	2.72 (0.23)
	MUR 5+GLY	168	82.29 (16.78)	86.56 (17.39)	4.27 (0.27)
	PLA+GLY	140	85.15 (19.96)	85.58 (20.74)	0.42 (0.29)
Combination with Met					
CV168022	MUR 2.5+MET	195	89.38 (19.10)	90.93 (19.89)	1.55 (0.23)
	MUR 5+MET	178	89.07 (19.34)	91.87 (20.24)	2.81 (0.24)
	PLA+MET	151	89.67 (17.49)	88.92 (17.90)	-0.75 (0.25)
CV168025	MUR 5+MET	512	90.31 (17.27)	91.79 (17.93)	1.47 (0.17)
	PIO 30+MET	473	90.95 (17.06)	91.57 (17.72)	0.62 (0.15)
All	MUR 5+MET	690	89.99 (17.82)	91.81 (18.54)	1.82 (0.14)

Dataset: Treated Subjects
* Prior to rescue.
Note: All subjects who had both baseline and week 24 measurements were included.

8.5.3 Hematologic Safety

Summary of Results

Decreases in hematological parameters have been noted as pharmacological effects of PPARγ agonists. They are believed to be due to hemodilution due to the fluid retention caused by these drugs.

Treatment with muraglitazar was associated with a modest decrease from baseline in hemoglobin, hematocrit, leukocytes, and ANC. The extent of reduction with the muraglitazar treatment was similar between the short term and LT treatment.

The incidence of anemia was low (< 1%) during muraglitazar therapy. The majority of events (except 2 SAEs) was reported as AEs; did not result in study drug discontinuation; and were without any clinical sequelae.

8.5.3.1 Anemia

Data on anemia are presented for 2 groups: 1) pooled data for subjects who received muraglitazar for up to 24 weeks either as monotherapy or as combination therapy, and 2) subjects who received muraglitazar for up to 104 weeks in the dose ranging monotherapy study.

The special search category MedDRA PT of 'anaemia' was used to define anemia. These cases of anemia were not necessarily confirmed by a hemoglobin level.

Short-term Phase 2 and 3 Studies; Muraglitazar up to 5 mg Dose (NDA Dataset)

During 24 weeks of treatment, the incidence of anemia for muraglitazar, placebo, and pioglitazone was 0.6%, 0.4%, and 0.6%, respectively.

- The majority of events (except 1 of 17 SAE for muraglitazar and 1 of 5 SAE for pioglitazone) were reported as non serious AEs.
- The study drug was not discontinued for the majority of subjects with anemia.

The SAE of anemia on muraglitazar 5 mg plus metformin is detailed below: on Day 82, the subject experienced a serious adverse event of anemia and on Day 85 the

subject was hospitalized and diagnosed with gastrointestinal bleeding. The event was reported as resolved on Day 85.

Long-term Dose Ranging Study (NDA Dataset)

The incidence of anemia for muraglitazar was lower than that for pioglitazone (0.7% versus 2.7%, respectively) during the LT phase.

- For both groups, none of the events were reported as SAEs.
- None of the subjects with anemia discontinued the study drug.

8.5.3.2 Hematologic Laboratory Parameters

Short-term Monotherapy, Muraglitazar up to 5 mg Dose (NDA Dataset)

Muraglitazar treatment was associated with a modest decrease from baseline in hemoglobin, hematocrit, leukocytes (Attachment 8.5.3.2A), and ANC at Week 24, which stabilized by 6-8 weeks after the start of treatment. Among various dose groups of muraglitazar (1.5, 2.5, and 5 mg), the reduction in these hematologic parameters appeared dose-related.

The reductions in hemoglobin and hematocrit with muraglitazar were comparable to those observed with pioglitazone. A greater reduction in leukocyte count and ANC was observed with muraglitazar than with placebo or pioglitazone.

Short-term Combination therapy

The results of the analyses of hematologic changes during combination therapy with sulfonylurea or metformin were consistent with those seen in monotherapy.

Long-term Monotherapy (NDA Dataset)

Consistent with the ST findings, the muraglitazar LT treatment was also associated with a modest decrease from baseline in hemoglobin, hematocrit, leukocytes, and ANC at Week 104 (Attachment 8.5.3.2B). The magnitude of the reductions seen after 104 weeks of treatment was similar as was seen after 24 weeks of treatment. This is consistent with the

observation in the ST studies that the hematologic levels stabilize after 6-8 weeks of treatment.

8.5.3.3 Absolute Neutrophil Count < 1000 cells/μL

The number of subjects with an ANC < 1000 cells/μL on 2 consecutive visits for subjects in muraglitazar treatment groups was low.

In the NDA Dataset, 1 subject on placebo, 1 on muraglitazar 1.5 mg, 2 on muraglitazar 5 mg, and 1 on muraglitazar 10 mg, had an ANC < 1000 cells/μL on 2 consecutive visits. These cases were not associated with any clinical sequelae and are detailed below:

- Subject CV168006-140-9 on muraglitazar 1.5 mg: This subject had ANC counts close to 1000 cells/μL at baseline (1125 cells/μL). The subject had several values of low neutrophil counts during the study. Study drug was discontinued on Day 393 due to neutropenia (720 cells/μl on Day 391). The subject had no symptoms associated with this event, specifically, no fever, chills, fatigue, shortness of breath, palpitations, or change in skin color.
- Subject CV168025-289-71 on muraglitazar 5 mg plus metformin: This subject had an ANC count of 1056 cells/μL at baseline. On Day 32 the ANC value was 960 cells/μL and was reported as an adverse event of worsening neutropenia. The subject had no signs or symptoms associated with infection. The subject was discontinued from the study on Day 35 due to the low ANC. ANC was 750 cells/μL and 740 cells/μL on Days 43 and 47, respectively. ANC tested at one, two, and three months post-discontinuation of study medication was 930 cells/μL, 350 cells/μL and 1090 cells/μL, respectively.
- Subject CV168006-233-8 on muraglitazar 5 mg: This subject had variable levels within the normal range throughout the study, and had 2 consecutive low counts on Days 751 (400 cells/μL) and 758 (593 cells/μL) of the study. The subject did not have any fever or signs of infection. Study medication was held from Day 765 through Day 769. The cell count returned to normal on Day 765 (2254 cells/μL) and the subject continued in the study.
- Subject CV168006-422-2 on muraglitazar 10 mg: On Day 280, the subject experienced an ANC of 846 cells/μL. The subject was still being treated with ciprofloxacin for a urinary tract infection which occurred on Day 243. Study medication was discontinued on Day 286 due to the neutropenia. The test was repeated on Day 287, which showed a decreased ANC of 764 cells/μL. A bone marrow biopsy was done on Day 290 (14-Feb-2003) and didn't show any pathological changes. A second follow-up sample collected on Day 301 showed an

ANC of 1361 cells/μL. The subject continued in the study, further cell counts were in the normal range.

- Subject CV168021-192-6 on placebo: This subject had normal levels at the beginning of the study (2662 cells/μL) and had an ANC < 1000 cells/μL on 3 occasions during the study (136 cells/μL on Day 27, 170 cells/μL on Day 81, and 392 cells/μL on Day 104). The cell count returned to normal on Day 110 (2597 cells/μL). Study medication was not interrupted.

8.5.4 Hypoglycemia

As would be expected with drugs that act as insulin sensitizers, hypoglycemia has not been noted to be an event of concern with PPARγ agonists when used as monotherapy.

The frequency of hypoglycemic events (symptoms of hypoglycemia accompanied with a fingerstick glucose level ≤ 50 mg/dL) was low. As expected, higher incidences were observed both for the muraglitazar and the placebo groups only in the combination with glyburide study, than in the other trials. The data for hypoglycemia are presented for the monotherapy and combination therapy studies (NDA Dataset).

The administration of muraglitazar 2.5 or 5 mg as monotherapy, or in combination with metformin, resulted in a low incidence in hypoglycemic events (Attachment 8.5.4). Hypoglycemic events occurred with similar frequency among the muraglitazar, placebo, and/or pioglitazone treatment groups. None of the hypoglycemic events required medical assistance (excluding management by subject and/or family member and/or friend usually with rapid-acting carbohydrate). Hypoglycemic events were slightly more frequent at the higher doses: 0.8% on 10 mg and 1.3% on 20 mg in the 24-week period of the dose ranging study. During the 104 week period of the dose ranging study few additional hypoglycemic events were observed.

Hypoglycemic events occurred more frequently when muraglitazar (2.5 and 5 mg) was administered in combination with sulfonylurea (7.3% and 10.4%, respectively) versus the combination of placebo with sulfonylurea (5.0%). Two subjects required medical intervention for hypoglycemia, 1 on muraglitazar 2.5 mg plus glyburide and the other on placebo plus glyburide.

In addition to the above reported hypoglycemic events, 3 SAEs of hypoglycemia were reported by a single investigator (2 subjects on muraglitazar 2.5 mg and 1 subject on muraglitazar 5 mg). All 3 subjects received intravenous glucose treatment for hypoglycemia with resolution of symptoms on the same day.

8.5.5 Renal Safety

PPARα agonists have been associated with a rise in serum creatinine levels. Renal safety was therefore evaluated by analyzing the mean change from baseline in serum creatinine levels and a threshold analysis of subjects reaching serum creatinine levels greater than 1.8 mg/dL (see Attachment 8.5.5). Both analyses showed that muraglitazar has no clinically meaningful effect on serum creatinine levels.

The mean change from baseline after 24-weeks for serum creatinine levels were analyzed for the Phase 3 studies. The results showed no clinically meaningful differences among the treatment groups (Table 8.5.5).

Table 8.5.5: Mean Change From Baseline in Serum Creatinine (mg/dL) at Week 24 (Phase 3 ST Studies)

	Placebo	Muraglitazar 2.5 mg	Muraglitazar 5 mg	Pioglitazone 30 mg
Monotherapy				
Baseline	0.81	0.84	0.82	--
Mean Change	-0.02	-0.03	0.00	--
Combination w/Glyburide				
Baseline	0.87	0.87	0.85	--
Mean Change	0.00	0.01	0.02	--
Combination w/Metformin				
Baseline	0.85	0.85	0.83	--
Mean Change	-0.01	-0.01	-0.01	--
TZD Comparator				
Baseline	--	--	0.82	0.81
Mean Change	--	--	0.03	0.04

8.5.6 Hepatobiliary Safety

Hepatobiliary safety was evaluated because an earlier PPARγ agonist, troglitazone was withdrawn from the market because of liver toxicity. In addition PPARα agonists, in particular fenofibrate, have been associated with a dose dependent increase in serum transaminase elevations. Furthermore, fibrates have been associated with an increase in gallstone formation.

8.5.6.1 Liver Function Tests

No signal of hepatotoxicity was detected in the muraglitazar clinical program. There were no cases of liver failure. Based on an assessment of the Complete Dataset, there were two subjects, treated with muraglitazar 1.5 and 2.5 mg, who had an ALT > 3 x ULN accompanied by a total bilirubin > 2 mg/dL. Both subjects were found to have acute cholecystitis and the enzymes returned to normal after treatment. Overall, across the entire dose range studied with muraglitazar, there were mean decreases from baseline in serum ALT and AST levels. Furthermore, the incidence of liver function test abnormalities associated with muraglitazar administration appears comparable to that of placebo or pioglitazone. Detailed results are presented below.

- One event of ALT > 3 x ULN plus total bilirubin > 2 mg/dL was reported for a muraglitazar 2.5 mg subject. This subject experienced non-serious epigastric distress on Day 38, mild in severity, and considered not related to study medication; she was treated with pantoprazole, scopolamine, and an antacid. On Day 42, she underwent an upper GI series procedure to determine the origin of her epigastric distress. The event resolved on Study Day 80. On Study Day 83 it was determined that she had gallstones, a non-serious AE of mild severity and not related to study medication. She completed participation in the study on Day 168. On Day 168, she had elevated liver enzymes (ALT: 543 U/L, bilirubin 2.8 mg/dL, AST 373 U/L, and alkaline phosphatase 295 U/L). She underwent a cholecystectomy on Day 176, and the event resolved on Day 183.
- One event of ALT > 3 x ULN plus total bilirubin > 2 mg/dL was reported for muraglitazar during the LT monotherapy. This subject receiving muraglitazar 1.5 mg had a history of gallstones. The subject experienced abdominal pain, vomiting, fever, chills, and jaundice (mild severity) on Day 324 (not related to the study drug). On Day 331, the subject had elevated ALT (152 U/L) and total bilirubin (2.4 mg/dL), which returned within normal limits on a repeat test on Day 338 (ALT: 44 U/L and total bilirubin: 1.00 mg/dL). Abdominal tomography and MRI revealed the presence

of gallstones. The investigator suggested that based on the symptoms, liver function test results, and imaging studies, it might be considered an acute cholangitis.

Mean Change From Baseline ALT, AST and Total Bilirubin: Short-Term and Long-Term Studies (NDA dataset)

Muraglitazar was associated with a mean decrease from baseline in liver function test parameters (ie, ALT, AST, and total bilirubin) (Attachment 8.5.6.1A and Attachment 8.5.6.1B). The reductions for muraglitazar were comparable to those for pioglitazone.

Incidence of Liver Function Test Abnormalities in Short-term Studies (NDA dataset)

ALT, AST, and total bilirubin: The incidence of elevated ALT, elevated AST, and elevated total bilirubin was lower for muraglitazar than that for placebo or pioglitazone (Table 8.5.6.1). None of the subjects on muraglitazar were discontinued due to an elevated ALT.

Table 8.5.6.1: Number (%) of Subjects with Liver Function Test Abnormalities During Study CV168006 ST+LT, 018 DB+OL, 021 ST+LT, 022 ST+LT and 025 ST+LT (Complete Dataset)

	Initial or Titrated Dose			
Parameter	ANY MUR=<5* N=2483	ANY MUR * N=2969	ANY PLA ** N= 528	ANY PIO=<45 N= 823
ALT (U/L)	n = 2413	n = 2895	n = 502	n = 806
ALT> 3*ULN	10 (0.4)	12 (0.4)	5 (1.0)	7 (0.9)
ALT> 5*ULN	2 (0.1)	2 (0.1)	1 (0.2)	3 (0.4)
ALT> 8*ULN	1 (0.0)	1 (0.0)	1 (0.2)	1 (0.1)
AST (U/L)	n = 2413	n = 2895	n = 503	n = 806
AST> 3*ULN	6 (0.2)	7 (0.2)	2 (0.4)	4 (0.5)
Total Bilirubin (mg/dL)	n = 2413	n = 2895	n = 502	n = 806
Bilirubin> 2 mg/dL	7 (0.3)	9 (0.3)	5 (1.0)	5 (0.6)
ALT (U/L) and Total Bilirubin (mg/dL)	n = 2413	n = 2895	n = 502	n = 806
ALT>3*ULN and Bilirubin> 2 mg/dL	2 (0.1)	2 (0.1)	0 (0.0)	0 (0.0)

Dataset: Treated Subjects
* Includes MUR 5 OL.
** Includes background therapy with secondary medication.
N = Number of subjects in the treatment group, n = number of subjects with available data.
Note: Includes post-treatment Lab. data up to the date of last treatment + 14 days. For CV168021 and CV168022 ST+LT, subjects who were randomized to placebo and titrated to muraglitazar 2.5 mg in the LT phase will have only data on placebo included.
One subject (CV168021-192-10) who had ALT > 3*ULN after titration from placebo to MUR 2.5 was not counted in the analysis.

8.5.6.2 Cholelithiasis

Cholelithiasis was evaluated because of the known increased risk with fibrates (PPARα agonists).

The incidence of cholelithiasis was low (< 1%) following the administration of muraglitazar as ST or LT therapy.

Data on cholelithiasis are presented for 2 groups: 1) pooled data for subjects who received muraglitazar for up to 24 weeks (ST phase) either as monotherapy or as combination therapy, and 2) subjects who received muraglitazar for up to 104 weeks (LT phase) as monotherapy.

Several MedDRA PTs were used to define cholelithiasis, these were: 1) 'cholelithiasis', 2) 'cholelithiasis obstructive', 3) 'gallbladder obstruction', 4) 'cholecystitis', 5) 'cholecystitis acute', 6) 'cholecystitis chronic', 7)'cholecystitis infective', 8) 'emphysematous cholecystitis', and 9) 'cholecystectomy.'

Cholelithiasis Short-term studies (NDA Dataset)

The incidence of cholelithiasis for muraglitazar ≤ 5 mg, placebo, and pioglitazone ≤ 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.

Cholelithiasis Long-term Dose-ranging Study (NDA Dataset)

The incidence of cholelithiasis for muraglitazar ≤ 5 mg and pioglitazone ≤ 45 mg was 0.9% (4 of 459) versus 0.7% (1 of 146) during the LT phase.

8.5.7 Muscle Safety

Muscle safety was carefully evaluated because of concerns with respect to myotoxicity observed with PPARα agonists. Professional labeling of fibrates and statins advise to avoid combining these drugs. Muscle safety is therefore analyzed separately for statin users and non-statin users. No clinical laboratory signal of myotoxicity was detected in the muraglitazar clinical program. Approximately 22% of subjects treated with muraglitazar were taking a statin.

Rhabdomyolysis

There was 1 case of reported rhabdomyolysis in a 55 year old male on muraglitazar 5 mg and glyburide who was asymptomatic and noted on routine labs to have an elevated CK of 4605 U/L with a peak level of 8513 U/L. The subject was not taking a statin or a fibrate and had been working in the yard. Several days later, the subject was admitted to the emergency room. At that time the CK level was 900 U/L while the subject remained on study medication. A cardiac workup was negative and the subject had a follow-up CK of 147 U/L eight days later.

CK mean change from baseline, Short-term studies: (NDA Dataset)

Muraglitazar ST treatment was associated with a mild increase in CK from baseline at Week 24 (Table 8.5.7A). These increases in CK were dose related. These changes were not influenced by statin use. The increases in CK levels for muraglitazar doses up to 5 mg were similar to those observed on pioglitazone.

Table 8.5.7A: Mean Change from Baseline in CK after 24 weeks (NDA Dataset)

		Placebo N = 528	Mura ≤ 5 mg N = 2374	Mura 10 mg N= 249	Mura 20 mg N = 237	Any Pioglitazone N = 823
With Statin	n	83	472	45	35	157
Baseline CK (U/L)		104.8	114.8	124.0	126.2	114.5
Mean Change from Baseline to Week 24		-5.67	2.52	19.78	23.31	10.82
No Statin	n	279	1408	151	136	475
Baseline CK (U/L)		117.4	118.7	113.5	125.7	103.4
Mean Change from Baseline to Week 24		10.24	8.53	4.88	35.85	10.40

Incidence of CK > 10 x ULN (Complete Dataset)

A small proportion of subjects had CK elevation > 10 x ULN. Across the entire dose range of muraglitazar this proportion was not different than with placebo. The incidence was also not influenced by the concomitant use of statins (see Table 8.5.7B). None of the muraglitazar-treated subjects with CK elevations had any symptoms of 'myalgia' or 'muscle ache.'

Table 8.5.7B: CK Elevations by Statin Use (Complete Dataset)

		Placebo	Mura ≤ 5 mg	Mura 10 mg	Mura 20 mg	Any Pioglitazone
With Statin	N	131	707	79	66	232
CK > 10x ULN, n (%)		0	1 (0.1)	0	0	0
No Statin	N	389	1730	166	171	580
CK > 10x ULN, n (%)		2 (0.5)	10 (0.6)	1 (0.6)	1 (0.6)	2 (0.3)

Concomitant Fibrate Use

A small proportion (1%) of subjects receiving muraglitazar received concomitant fibrate therapy, preventing any conclusion about the safety of muraglitazar in combination with fibrates.

8.6 Safety in Special Groups and Situations

8.6.1 Intrinsic Factors

8.6.1.1 Age, Gender, Race, Ethnicity, and Other Baseline Characteristics

The extent of exposure, demographic and baseline characteristics, common AEs (≥ 5%), and marked laboratory abnormalities for all subjects with type 2 diabetes (muraglitazar up to 5 mg dose, pooled) have been analyzed by age (< 65 years, ≥ 65 years), gender (male, female), race (White, Black, other), and ethnicity (Hispanic/Latino, non Hispanic/Latino). No apparent clinically relevant differences were noted in the extent of

exposure, demographic and baseline characteristics, AE profile (either as specific clinical AEs or as a specific system organ classes), and incidence of marked abnormalities among the muraglitazar, placebo or pioglitazone treatment groups based on these subgroups.

The incidence of edema-related events by subgroups is presented in Section 8.5.1. The incidence of edema-related events seems to be higher in subjects with greater BMI and insulin levels at baseline for both the muraglitazar- and pioglitazone-treated subjects.

8.6.1.2 Renal and Hepatic Impairment

Renal elimination of muraglitazar is minimal (< 5%), suggesting that renal impairment is unlikely to alter the pharmacokinetics of muraglitazar. No dose adjustment in subjects with renal dysfunction is recommended.

The pharmacokinetics of muraglitazar in subjects with mild hepatic impairment (Child-Pugh A) was similar to age-, gender-, and BMI-matched healthy subjects. Subjects with moderate to severe impaired hepatic function (Child-Pugh B/C) have a ~2-3 fold increase in AUC values compared to healthy subjects. Muraglitazar should not be initiated in subjects with active liver disease.

8.6.2 Extrinsic Factors

Use of Statin or Fibrate

During the clinical program approximately 22% of subjects treated with muraglitazar were taking a statin. There was no evidence of a drug interaction based on PK studies (see Attachment 5). In addition, there was no clinical evidence of muscle toxicity with co-administration of statins (see Section 8.5.7).

Very few subjects (~1%) in the muraglitazar clinical program were using concomitant fibrates, and therefore the safety of concomitant use could not be established. Since muraglitazar and fibrates both act through PPARα agonism, concomitant use of muraglitazar and a fibrate is not currently recommended.

Food Effect

There was no effect of gastric acid suppression on the pharmacokinetics of muraglitazar;

a single oral dose of famotidine did not alter either the Cmax or AUC of muraglitazar. Although a high fat meal decreased Cmax by 33% without changing the AUC of muraglitazar, this blunting of Cmax alone is not thought to be clinically significant. There were no evident differences in safety or tolerability between fasted and fed administration. Thus, muraglitazar may be administered with or without food.

Tobacco or Alcohol Use

An analysis on use of tobacco or alcohol consumption was not performed in the muraglitazar program.

8.7 Summary of Safety

Treatment with muraglitazar in subjects with type 2 diabetes was generally well tolerated. The following are the key safety and tolerability findings from the development program:

- Consistent with its mechanism of action, treatment with muraglitazar resulted in dose-dependent weight gain. Mean weight gain at 24 weeks with the 2.5 and 5 mg doses ranged from 1.1 kg to 4.3 kg, respectively, in Phase 3 trials. Weight gain was an infrequent cause of subject discontinuation.
- Consistent with its mechanism of action, treatment with muraglitazar was associated with dose-dependent increases in the incidence of edema-related AEs. Most events were mild to moderate in severity and few subjects discontinued due to edema-related AEs.
- Consistent with its mechanism of action, treatment with muraglitazar was associated with infrequent reports of heart failure. Heart failure events, whether investigator-reported or identified through adjudication, were generally recognizable, insidious in onset, and manageable, often resolving with diuretic or other medical treatment, and did not necessarily require discontinuation of muraglitazar therapy. Adjudication of heart failure and related AE terms did not result in identification of a new serious heart failure event in any subject in the Phase 3 clinical program.
- No difference in the cumulative incidence of CV adverse events was observed between muraglitazar treatment and placebo, based on a Kaplan-Meier analysis incorporating all data available to date from the Complete Dataset. An imbalance in CV events was observed within a single study (CV168021), but this imbalance was not observed in the other 4 studies in the Phase 2/3 clinical program.
- A total of 21 deaths were reported in the muraglitazar clinical program. None of the deaths reported was considered related to the study drug by the investigators. An

imbalance in deaths was observed within a single study (CV168025), but this imbalance was not observed in the other 4 studies in the Phase 2/3 clinical program.

- There was no signal for any excess of malignancies in subjects treated with muraglitazar compared to subjects receiving placebo or pioglitazone. No difference in the incidence of bladder cancer was observed between muraglitazar and pioglitazone control groups.
- No signals for hepatobiliary, renal or muscle toxicity were detected with muraglitazar treatment as monotherapy or combination therapy, or when coadministered with a statin.
- Consistent with its mechanism of action, treatment with muraglitazar was not associated with clinically significant reports of hypoglycemia when used as monotherapy or in combination with metformin. As expected, dose-dependent hypoglycemia occurred in subjects taking muraglitazar in combination with a fixed dose of a sulfonylurea, glyburide.
- No new safety concerns have emerged in subjects receiving muraglitazar as monotherapy or in combination based on analysis of long-term safety data accumulated after the submission of the muraglitazar NDA.

Based on the results of the muraglitazar Phase 2/3 clinical program, which evaluated doses up to four times the maximum recommended dose of 5 mg, the overall profile of adverse events with muraglitazar in type 2 diabetes subjects was similar to those previously observed with the TZD PPARγ agonists. Most side effects did not result in subject discontinuation, and serious side effects occurred infrequently. No new safety signals were observed with longer term exposure to muraglitazar.

9 ON-GOING AND PLANNED NON-CLINICAL AND CLINICAL STUDIES

9.1 Non-clinical Studies

Non-clinical investigative toxicology studies have been conducted to investigate the mechanism of the urinary bladder tumorigenic response in male rats administered muraglitazar since transitional cell tumors occurred at relatively low multiples (approximately 8 times) of human exposure at a clinical dose of 5 mg/day.

Data from non-clinical studies completed support crystalluria as the mode of urinary bladder tumor development in rats, a mechanism not relevant to humans. All other drug-related tumors were considered to be of no established clinical relevance because they were observed at suprapharmacologic exposures in excess of 48 times the exposure observed at a clinical dose of 5 mg and because safety margins at the highest non-tumorigenic dose were ≥ 17 times the human exposure at 5 mg.

9.2 Randomized Clinical Studies

9.2.1 Ongoing Randomized Clinical Studies

Five clinical studies are currently ongoing and will provide additional safety data and durability of effect data beyond the large and comprehensive data base included in the NDA. These studies include:

- 1 long term (4 years) extension study at multiple muraglitazar dose levels (dose ranging study)
- 1 long-term (2 years) extension of the glyburide combination study
- 1 longterm (2 years) extension of the metformin combination study
- 1 1-year study in combination with metformin at doses up to 10 mg, which includes an echocardiographic sub-study.
- 1 ST study in drug-naive subjects at doses up to 10 mg.

9.2.2 Planned Randomized Clinical Studies

Three clinical studies are planned which will, when completed, provide additional information in sub-populations of type 2 diabetes patients. These studies will provide data on the use of muraglitazar in important type 2 diabetic subpopulations not yet studied in the clinical trial program that may benefit from treatment with muraglitazar, even in the face of possible risks. One of these studies will be conducted in the elderly and 1 in diabetes patients with pre-existing heart failure (NYHA Class I and II). Additionally, 1 study will evaluate the safety and efficacy of muraglitazar co-administered with insulin.

All clinical studies will include comprehensive evaluation of past medical history and use of concomitant medications to allow for risk stratification by factors that may increase the risk of heart failure. The Sponsors will continue to collect and evaluate data from these studies for any adverse events related to serious muscle toxicity including rhabdomyolysis, events of bladder cancer and other malignancies. In addition, sampling for biomarkers, including NT-proBNP, and for use in future pharmacogenetic studies will be performed to further inform this risk factor analysis.

9.2.3 Long-Term Cardiovascular Outcomes Trial

Overall, substantial and pivotal efficacy in glycemic and lipid control in type 2 diabetes has been demonstrated in the muraglitazar clinical program. Nevertheless, potential benefits for cardiovascular morbidity and mortality outcomes in type 2 diabetes can not be completely understood until more prolonged clinical experience is collected. Clinical knowledge regarding how treatment with PPARγ and PPARα activators impact cardiovascular and other clinical outcomes in type 2 diabetes will expand with release of findings from 2 clinical outcomes studies with pioglitazone (PROACTIVE) and fenofibrate (FIELD).[33,34] To evaluate the long-term benefit-risk profile of muraglitazar, and in particular the impact of long-term treatment with muraglitazar on cardiovascular morbidity and mortality, a long-term clinical outcomes study is being planned. This study will elucidate the benefits of muraglitazar beyond its significant effect on established surrogate markers of A1C, HDL-C and TG and on other CV biomarkers such as hs-CRP and PAI-1, relative to the propensity to cause fluid accumulation that, in a very small subset of vulnerable patients, may result in symptoms of heart failure. The specific design of the muraglitazar cardiovascular outcomes study will depend on the results of the PROACTIVE and FIELD studies, which are due to report later this year as well as pending data on muraglitazar 10 mg as a titration dose and muraglitazar in combination with insulin.

9.2.4 Phamacogenetic Studies

To identify potential individual risk factors associated with development of edema, heart failure or weight gain in subjects treated with muraglitazar, exploratory pharmacogenetic analyses of available data from subjects in Phase 2 trials were performed. To date, 750 subjects were genotyped for 250 single nucleotide polymorphisms (SNPs) in 114

candidate genes. Sixteen hundred additional samples will be analyzed from Phase 3 trials. Candidate genes selected were broadly classified as those expressed in the kidney (renin-angiotensin-aldosterone system), heart (adrenergic receptors), and vascular tissue (endothelin). Suggestive associations between SNPs and increased risk of these adverse events will be further examined as part of the pharmacovigilance plan. These pharmacogenetic studies may allow us to gain additional understanding of the mechanisms related to development of edema, heart failure or weight gain, and possibly to identify a genetic profile that may contribute to increased individual susceptibility to these risks, either alone or in combination with other risk factors.

10 PHARMACOVIGILANCE PLAN

In clinical Phase 2/3 studies, approximately 2969 subjects with type 2 diabetes were treated with muraglitazar, including doses up to four times the maximum recommended dose of 5mg. Long-term data included 697 subjects treated with muraglitazar for at least 104 weeks. The safety profile of muraglitazar observed in this program was qualitatively similar to pioglitazone, and was consistent across diverse studies and diverse populations of diabetics, suggesting a predictable safety profile that will be broadly applicable to the target population anticipated in general practice. However, since phase 2/3 clinical studies are limited in terms of detecting rare adverse events or adverse events appearing after long latency periods, it is important to continue to assess the long-term benefits and risks of treatment in a more general population under the conditions of usual clinical care.

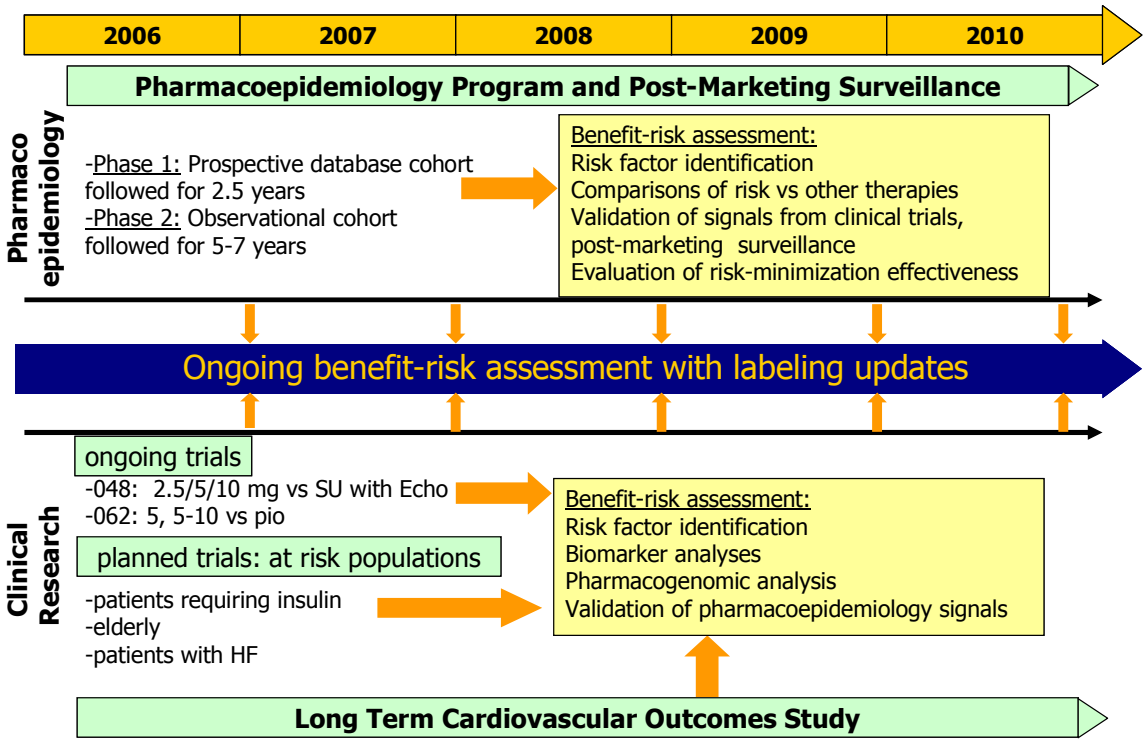
The Sponsors are committed to undertaking good pharmacovigilance practices as put forth in the March 2005 FDA Guidance for Industry, which states: Since it is impossible to identify all safety concerns during clinical trial programs, and there is usually a large increase in patients exposed to a new treatment including those with a broader range of co-morbid conditions and those taking a wider range of concomitant medications than subjects included in clinical trials, it is important to continue to evaluate and characterize the risk profile of a new treatment in the postmarketing period.

In recognition of this, the Sponsors have designed a comprehensive pharmacovigilance plan which includes enhanced post-marketing surveillance of spontaneous adverse event reports, randomized controlled trials in special type 2 diabetic populations including

elderly patients and patients with Class I or Class II heart failure, continued safety monitoring of adverse events of special interest in all ongoing and planned clinical trials, and a large observational study to detect increased risks of unexpected adverse events that are rare or that may only occur after an extended period of exposure.

The pharmacovigilance plan timeline is presented in Figure 10 and is described in greater detail below. As seen in this figure, the Sponsors is committed to on-going benefit-risk assessment through studies that seek to document benefit in a broader range of patients and related to long-term cardiovascular outcomes, to more specifically characterize known risks and risk factors, and to evaluate ways to further minimize risk, while continually monitoring the safety profile of muraglitazar in both randomized controlled trials as well as in the actual practice setting.

Figure 10: Muraglitazar Pharmacovigilance Plan Timeline



10.1 Post-Marketing Surveillance

Routine post-marketing surveillance of adverse events reported to the Sponsors through spontaneous AE reporting systems will be enhanced by the following activities:

- All spontaneously reported serious and nonserious adverse events will be reviewed, with special attention paid to serious, unlabeled AEs and AEs of special interest such as heart failure and other serious cardiovascular events, rhabdomyolysis, particularly in combination with statins, and malignancy. activities will be focused on evaluation for adequacy of information, biologic plausibility, and whether additional information is required to evaluate the event(s) in the context of the patient's other medical conditions and concomitant medications, such as for serious adverse events that have been identified for close scrutiny, the Sponsors may directly contact the reporting health care professional to obtain follow-up information. For selected events, including AEs of special interest, on which periodic aggregate data analyses may be performed, a standardized set of queries will be used. Published literature will also be searched for cases of these events in patients treated with muraglitazar and other PPAR activators.
- Post-marketing review for safety signal detection will be performed on a periodic basis as one means of tracking the above adverse events of interest in the post-approval period. On an annual basis, spontaneous reporting rates of selected events including AEs of special interest will be estimated. In addition, rates of these events will be calculated per 1000 patient years of exposure from aggregate clinical trial data. Significant changes in frequencies will be communicated to FDA and addressed with appropriate modifications to product labeling, as necessary. Annual listings and analyses from the observational study described below will be provided to FDA annually, including formal relative risk analyses when 1000, 5000 and 10,000 patient years of muraglitazar exposure are reached.

The Sponsors will prepare periodic aggregate reports (US NDA Periodic Reports and Periodic Safety Update Reports) quarterly and every 6 months, respectively, for the first 5 years post-approval. All relevant data will be reviewed by the Sponsors and described in the context of the total muraglitazar experience.

10.2 Pharmacoepidemiology Observational Study

As discussed above, due to the limitations in size, duration of exposure, and breadth of patient populations in clinical trials, it is impossible to detect adverse events of low frequency, long latency or that may occur within a wider range of patients during the pre-marketing assessment period. Furthermore, proper dosing represents an important

strategy for optimizing benefit and minimizing risk of muraglitazar in treatment of type 2 diabetic patients. Therefore, the Sponsors proposes to conduct a prospective observational study of adult patients with type 2 diabetes eligible to be treated with muraglitazar, in order to assess the safety profile of muraglitazar in the general population under conditions of usual care, and to monitor the appropriate use of muraglitazar in relation to starting dose, dose titration, and management of treatment-emergent heart failure.

This observational study will be conducted using a large managed care database representing approximately 4.5% of diabetics diagnosed in the US. Approximately 5,000 diabetic patients treated with muraglitazar and 10,000 patients treated with other antidiabetic agents will be enrolled and followed for a minimum of 5-7 years. Patients will be assigned to 1 of 4 groups: a muraglitazar treated group and three groups reflecting standard of care (an oral antidiabetic group with no TZD treatment, an oral antidiabetic group with recently prescribed TZD treatment and a group with insulin treatment). Patients will also be stratified into TZD naïve (ie, not previously treated with a TZD) and TZD-treated (ie, previously treated with a TZD) patient populations. Data on unexpected events such as cancer or rhabdomyolysis, or adverse events of special interest will be collected annually from the managed care database or from patients who may have dropped out of the database, for a total of approximately 7 years per patient. Incidence rates will be computed annually for the muraglitazar-treated and otherwise-treated patients. This study will provide insight into the risk/benefit profile of muraglitazar in the general population, and will have the power to detect a two fold increase or decrease in the risk of bladder cancer after 5 years of follow-up. In addition, data on prescribing patterns in relation to dosing will be collected quarterly to monitor for appropriate use of muraglitazar in usual practice.

Further details of the study design are still in development, and a draft synopsis stating the general framework of the proposed study has been submitted to the FDA. Final study protocol and timelines will be discussed with the FDA and epidemiology experts prior to implementation of the study.

10.3 Randomized Clinical Trials in Special Populations

Two clinical studies are planned which will, when completed, provide additional safety information in sub-populations of type 2 diabetics, including the elderly and those with pre-existing heart failure (NYHA Class I and II). Additionally, 1 study will evaluate the safety and efficacy of muraglitazar co-administered with insulin.

10.4 Safety Monitoring in Randomized Controlled Trials

All clinical studies will include comprehensive evaluation of past medical history and use of concomitant medications to allow for risk stratification by factors that may increase the risk of heart failure or other events associated with muraglirtazar in vulnerable patients. The Sponsors will continue to closely monitor, collect and evaluate data from these studies for any unexpected adverse events or adverse events of special interest. In addition, sampling for biomarkers, including NT-proBNP, and for pharmacogenetic studies, will be performed to further inform this risk factor analysis

10.4.1 Pharmacogenetic Studies

To identify potential individual risk factors associated with development of edema, heart failure or weight gain in patients treated with muraglitazar, exploratory pharmacogenetic analyses of available data from patients in Phase 2 trials were performed. To date, 750 patients were genotyped for 250 single nucleotide polymorphisms (SNPs) in 114 candidate genes. Sixteen hundred additional samples will be analyzed from Phase 3 trials. Candidate genes selected were broadly classified as those expressed in the kidney (renin-angiotensin-aldosterone system), heart (adrenergic receptors), and vascular tissue (endothelin). Suggestive associations between SNPs and increased risk of these adverse events will be further examined as part of the pharmacovigilance plan. These pharmacogenetic studies may allow us to gain additional understanding of the mechanisms related to development of edema, heart failure or weight gain, and possibly to identify a genetic profile that may contribute to increased individual susceptibility to these events, either alone or in combination with other risk factors.

11 OVERALL BENEFIT/RISK EVALUATION AND CONCLUSIONS

Since the publication of the findings of the DCCT and the UKPDS, it has become clear that intensive diabetes management to achieve tighter hyperglycemic control can result in significant reduction in the development and progression of microvascular complications of diabetes.[5,45] These complications are progressive and debilitating and include blindness due to retinopathy, amputation due to neuropathy and attendant peripheral vascular disease, and kidney failure and the need for renal transplantation due to nephropathy.[46] Furthermore, although not demonstrated directly with the TZD PPARγ agonists, the frequency of cardiovascular and macrovascular complications such as myocardial infarction, other cardiac disease and stroke is also decreased by near-normalization of blood glucose levels. The positive impact of tight glycemic control has perhaps been shown most dramatically at a recent presentation at the June 2005 ADA meeting. There, LT follow up of the original DCCT/EDIC cohort of type 1 diabetic patients evaluated the impact of intensive antihyperglycemic control on cardiovascular disease.[7] This study demonstrated a 57% reduction in the number of serious cardiovascular events such as myocardial infarctions and strokes among type 1 diabetes patients whose glycemic control was tightly managed to an A1C target of < 7% for 6.5 years during the original DCCT study, even though they had subsequently relaxed their glycemic control to similar to the conventional control group with a mean A1C value of approximately 8% since the formal study ended 10 years earlier.

These findings have established near-normalization of glucose control as a fundamental component of the management of diabetic patients, and WHO and ADA guidelines define a target goal for A1C lowering either to < 6.5% or < 7%. Whatever the numeric A1C goal, the overarching objective of achieving tight A1C glycemic control for diabetes patients, especially without the propensity to cause significant hypoglycemia, is clearly important because the microvascular and macrovascular morbidities of type 2 diabetes constitute a large medical need and contribute greatly to overall US health care costs.

In addition to suffering from hyperglycemia, 67% of adults with type 2 diabetes have one or more lipid abnormalities such as elevated triglycerides and reduced HDL-C and have a 2-to 4-fold increased risk of macrovascular diseases such as myocardial infarction and

stroke. Results of the VA-HIT study with the PPARα agonist gemfibrozil demonstrated a 32% relative risk reduction (p = 0.004) for major cardiovascular events including non-fatal MI, coronary heart disease (CHD) death and stroke[17] in a subset of type 2 diabetic patients with dyslipidemia. Multivariate analyses from this study indicated that for every 5 mg/dL increase in HDL-C, CHD events were reduced by 11%. The effect of fenofibrate treatment on progression of coronary artery disease in type 2 diabetes was examined in the Diabetes Atherosclerosis Intervention Study.[47] Fenofibrate treatment significantly reduced progression of atherosclerotic lesions in this angiographic study. There was a 23% risk reduction associated with fenofibrate treatment for the combined endpoint of death, MI, coronary angioplasty, coronary artery bypass surgery and angina, although this was not statistically significant. Therefore, in addition to hyperglycemia, there remains a medical need for improvement of lipid abnormalities associated with diabetes.

11.1 Summary of Benefits

The benefits of muraglitazar as monotherapy and as combination therapy in the treatment of type 2 diabetes are clinically meaningful and are substantiated by:

- Large and clinically significant reductions in A1C and fasting plasma glucose (FPG) levels at the 2.5 mg and 5 mg doses of muraglitazar (all 5 pivotal studies).
- Very large reductions (-2.6%) in A1C in diabetic subjects with high baseline A1C levels (> 10.0% and ≤ 12.0%) at the 5 mg dose of muraglitazar in the open-label cohort of monotherapy study CV168018.
- Achievement of glycemic targets (defined as A1C < 7%) in the majority of subjects (ranging from 52.3% to 71.8%) at the 2.5 mg and 5 mg doses of muraglitazar (all studies).
- Sustained efficacy as shown by maintenance of reduced A1C to levels below glycemic goals for at least 2 years in monotherapy study CV168006 and for at least 50 weeks as combination therapy with metformin in study CV168025.
- Reductions in several metabolic indicators of insulin resistance (fasting insulin, fasting C-peptide, and FFA levels) (all studies).
- Improvements in lipid parameters of diabetic dyslipidemia, including increasing HDL-C, and decreasing TG, apoB, and non-HDL-C levels.

These benefits of muraglitazar in the treatment of type 2 diabetes derive from its mechanism of action as a dual α/γ PPAR agonist with balanced activity overall at these related receptor targets. PPARγ effects on both glycemic and insulin sensitivity

parameters (reducing A1C, FPG, fasting insulin, fasting C-peptide, and FFAs) and PPARα effects on key lipid parameters (reducing TGs and apoB and increasing HDL-C) are demonstrated at both muraglitazar 2.5 mg and 5 mg doses. These dual efficacy features of muraglitazar are dose-related, and thus it is anticipated that the need to add efficacy for reaching glycemic A1C targets and/or for increasing lipid efficacy in patients with diabetic dyslipidemia can be achieved by treating with muraglitazar 5 mg initially or after starting with the 2.5 mg dose and titrating to the higher dose. Future clinical studies are also addressing efficacy relative to safety and tolerability of titrating from muraglitazar 5 mg to 10 mg in appropriate patients, possibly as a step to further maintain durable efficacy before adding other treatments such as insulin. Ultimately, assuming that prior landmark trial results like UKPDS, DCCT/EDIC and VA-HIT (and possibly other imminent trial results from PROACTIVE and FIELD) are relevant, then LT efficacy for key diabetic metabolic and cardiovascular morbidities should also be impacted favorably by treatment with muraglitazar. Confirmation of this prediction will be assessed with the planned LT cardiovascular morbidity and mortality study described in Section 10.

11.2 Summary of Risks

The safety profile of muraglitazar has been well characterized. Both the 2.5 mg and the 5 mg dose have an acceptable safety and tolerability profile. The following are the key safety findings observed during the clinical development program of muraglitazar:

- Heart failure has been identified as the most important risk with muraglitazar treatment. Overall heart failure was infrequent in the muraglitazar program, occurring in 0.19% of subjects receiving muraglitazar 2.5 mg and 0.34% of subjects receiving muraglitazar 5 mg, confirming a dose relationship observed with PPARγ agonists. Heart failure appeared to be easily recognizable, treatable with diuretics and/or muraglitazar discontinuation, as well as reversible. Subjects with a history of heart failure or a history of an atherosclerotic cardiovascular event appeared to be at increased risk for heart failure.
- Treatment with muraglitazar resulted in dose-dependent weight gain as is expected with PPARγ agonist activity. The median weight gain was comparable for muraglitazar 2.5 mg and pioglitazone 15 mg (+1.0 kg and +0.9 kg, respectively). Median weight gain at the end of 24 weeks of treatment for both monotherapy studies was higher with muraglitazar 5 mg (+2.2 kg) than with either pioglitazone 15 mg (+0.9 kg) or placebo (-0.3 kg).

- The incidence of edema-related AEs was dose-dependent and higher for muraglitazar than for placebo when administered either as monotherapy or combination therapy. Most of these events were mild to moderate in severity and very few subjects were discontinued due to edema-related AEs.
- There were no safety signals for liver, muscle, or kidney toxicity.

Based on the results of the muraglitazar clinical trial program, which evaluated doses up to four times the maximum recommended dose of 5 mg, the overall profile of adverse events with muraglitazar, in type 2 diabetes subjects, was expected based on prior observations with the TZD PPARγ agonists.

11.3 Conclusions

Muraglitazar 2.5 mg and 5 mg demonstrate an overall efficacy and safety dose range profile that is similar to that seen with marketed PPARγ agonists. Specifically, on the benefit side, the dose choice offered by muraglitazar 2.5 mg and 5 mg as either monotherapy or in combination with metformin or sulfonylureas demonstrates glycemic efficacy and specific TG lowering and HDL-C raising lipid efficacy. This set of muraglitazar doses enables meaningful percentages of subjects to reach important A1C and lipid treatment goals for type 2 diabetes mellitus and to maintain durability of these key efficacy parameters over time.

Events that are recognized as side effects of the TZD PPARγ agonists were also observed with muraglitazar. Muraglitazar also possesses PPARα agonist activity, but no signals of myotoxicity or hepatobiliary toxicity, including excess gallstone formation, were observed. This experience includes data on subjects who were concurrently treated with statins, which comprised up to 24% of the type 2 diabetes subjects studied in the muraglitazar combination studies.

Both the muraglitazar 2.5 mg and 5 mg doses were used as starting doses in parallel arm studies for the Phase 3 clinical development program. Efficacy results in both monotherapy and combination therapy demonstrated that the 2.5 mg dose is effective but the 5 mg dose will enable a greater percentage of patients to achieve A1C goals. At high baseline A1C levels above 10%, muraglitazar 5 mg provided substantial glycemic

efficacy and enabled many subjects to reach target A1C goals. Likewise, both the 2.5 mg and 5 mg doses also provided TG and HDL-C benefits.

Although events related to fluid retention and infrequent events of heart failure occurred more often on the 5 mg dose relative to the 2.5 mg dose, the qualitative safety and tolerability profiles for these 2 doses were similar overall. For all five clinical trials involving monotherapy and combination therapy in subjects with type 2 diabetes, precipitation or exacerbation of heart failure events by muraglitazar, in particular, was qualititatively similar regardless of dose, including subjects randomized to 10 or 20 mg in the dose-ranging study. An evaluation of underlying cardiac and other risk factors prevalent among the type 2 diabetes population in the muraglitazar clinical program indicated that patients with a history of heart failure or a history of a cardiovascular event have a greater probability to develop heart failure. Furthermore the incidence of heart failure was dose dependent and lower with monotherpay than with combination therapy.

Therefore, both muraglitazar 2.5 mg and 5 mg are recommended as potential alternative starting doses, albeit with important distinctions. Muraglitazar 2.5 mg will represent an appropriate starting dose for subjects with mild degrees of hyperglycemia. The muraglitazar 2.5 mg dose is also the appropriate dose in subjects suspected to be less tolerant to fluid overload, such as subjects with New York Heart Association (NYHA) Class II heart failure or possibly other significant risk factors for heart failure. Given overall benefit/risk considerations, muraglitazar 5 mg represents a more suitable starting dose choice for markedly hyperglycemic and/or hyperlipidemic diabetes subjects requiring greater initial glycemic and diabetic dyslipidemia efficacy.

The recommended labeling of muraglitazar will advise not to use muraglitazar in patients with NYHA III and IV heart failure. In diabetes patients with NYHA Class II heart failure, initiation of dosing with muraglitazar 2.5 mg is recommended. Advice will also be given not to use muraglitazar in patient treated with insulin or in type 2 diabetes patients younger than 18 years of age because it has not been studied in these patient populations at the present time. Finally, muraglitazar will not be recommended for use with either thiazolidinediones or fibrates.

Using these dosing recommendations, patients will derive optimal benefit for achieving glucose control and lipid improvements while minimizing important side effects that

have been recognized for other TZD PPARγ agonists and have been confirmed to occur with muraglitazar treatment in a dose-dependent manner. The opportunity to choose among 2 starting doses will allow patients and physicians to consider and apply an informed risk/benefit evaluation to optimize management of type 2 diabetes. Minimization of risk for PPARγ mediated side effects is achievable by starting patients at 2.5 mg dose. Starting or titration to the 5 mg dose should be considered for patients who need robust glycemic or lipid control.

The overall benefit/risk profile of muraglitazar in the clinical trial program is favorable, based on:

1) A high percentage of subjects reaching the A1C goals with evidence of durability in long-term follow-up.
2) High degrees of glycemic efficacy, even when diabetes subjects are poorly controlled, as demonstrated by the large -2.6% AIC decrease in subjects with initial A1C levels between 10% and 12%.
3) Significantly decreased TG and significantly increased HDL-C levels compared to placebo in monotherapy and in combination with glyburide or metformin.
4) Manageable, infrequent risk of heart failure, a clinical event that is recognizable and reversible in most cases with adjunctive treatment such as diuretics and/or cessation of muraglitazar.

Overall, the proven benefits of muraglitazar, when considering its efficacy against the current TZDs, support its use for the proposed indications.

12 LIST OF DEFINITIONS

Term	Definition
α	alpha
δ	delta
γ	gamma
AACE	American Association of Clinical Endocrinologists
A1C	hemoglobin A_{1c} (glycosylated hemoglobin)
ADA	American Diabetes Association
AE	adverse event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ANCOVA	analysis of covariance
apoB	Apolipoprotein B
AST	Aspartate transaminase
AUC	area under the curve
BMS	Bristol-Myers Squibb
BMS-298585	muraglitazar
BNP	Brain natriuretic paptide
BrdU	bromodeoxyuridine
CDC	Centers for Disease Control
CHD	Coronary heart disease
CHF	congestive heart failure
CI	Confidence interval
CK	creatine kinase
Cmax	maximal drug concentration
CSR	Clinical study report
CV	cardiovascular
CVD	Cardiovascular disease
CYP	cytochrome P450
DCCT	Diabetes Control and Complications Trial
ECG	electrocardiogram

Term	Definition
EDIC	Epidemiology of Diabetes Interventions and Complications
FDA	Food and Drug Administration
FFA	free fatty acids
FPG	fasting plasma glucose
HDL-C	high-density lipoprotein cholesterol
HOMA-IR	Homeostatsis model assessment - insulin resistance
HOMA-%B	Homeostatsis model assessment - beta cell function
hs-CRP	Highly sensitive C-reactive protein
KM	Kaplan-Meier
LDL-C	low-density lipoprotein cholesterol
LOCF	Last observation carried forward
LT	Long-term
MDG	mean daily glucose
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MUR	muraglitazar
non-HDL-C	non-high-density lipoprotein cholesterol
NCEP	National Cholesterol Education Program
NDA	New Drug Application
NYHA	New York Heart Association
OL	Open label
PD	pharmacodynamic
PAI-1	Plasminogen activating factor-1
PIO	pioglitazone
PK	pharmacokinetic
PLA	placebo
PPAR	peroxisome proliferator-activated receptor
PT	preferred term
QD	Qua′que di′e (Latin abbreviation for every day)
QTc	QT corrected
QTcF	QT interval corrected by the Fridericia method

Term	Definition
SAE	serious adverse event
SNP	single nucleotide polymorphisms
SOC	system organ class
ST	short-term
SU	sulfonylurea
TG	triglyceride
TZD	thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study
ULN	Upper limit of normal
US	United States of America
VA-HIT	Veterans Affairs high-density lipoprotein intervention trial
WBC	White blood cell count

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Attachment 3.1A: CV168008 ST Synopsis

10 page(s) excluding cover page

Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient: Muraglitazar (BMS-298585)		

SYNOPSIS

Clinical Study Report CV168008 - Short-Term Phase

TITLE OF STUDY: A Randomized, Double-Blind, Dose-Ranging, Placebo-Controlled Trial to Determine the Lipid-Lowering Efficacy and Safety of BMS-298585 Alone and in Combination with Pravastatin in Subjects with Mixed Dyslipidemia: Results of 6-Week, Double-Blind Phase

INVESTIGATORS: Fifty (50) investigators participated in the conduct of this study.

STUDY CENTERS: Fifty (50) centers in the United States of America were involved in the conduct of this study.

PUBLICATIONS: None.

STUDY PERIOD: Date first subject enrolled: 5-Feb-2002

Date last subject completed: 06-Aug-2002 (for the short-term 6 week double-blind treatment phase)

CLINICAL PHASE: 2b/3

OBJECTIVES: The primary objective was to compare, at a 0.05 level of significance, after 6 weeks of oral administration of double-blind treatment, the percent change from baseline in average fasting triglyceride (TG) level at Weeks 5 and 6 (Week 5/6) between 5 mg, 10 mg, and 20 mg doses of BMS-298585 alone versus placebo in subjects with mixed dyslipidemia and on a stable National Cholesterol Education Program (NCEP) Step I diet.

Secondary objectives of this study (6-week, double-blind phase only):

- To assess, after 6 weeks of oral administration of double-blind treatment, changes in serum total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), non-HDL-cholesterol (non-HDL-C), apolipoprotein (Apo) A1, ApoB, fasting free fatty acid (FFA), systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), body weight, glycosolated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), fasting insulin, fructosamine and health assessment achieved with 5 mg, 10 mg and 20 mg doses of BMS-298585 alone versus placebo.
- To assess, after 6 weeks of oral administration of double-blind treatment, changes in serum TG, TC, HDL-C, LDL-C, non-HDL-C, $ApoA_1$, ApoB, fasting FFA, SBP, DBP, BMI, body weight, HbA_{1c}, FPG, fasting insulin, and fructosamine achieved with 20 mg BMS-298585 in combination with 40 mg pravastatin versus 20 mg BMS-298585 alone and versus placebo.
- To assess after 6 weeks of oral administration of double-blind treatment, changes in fasting insulin, glycemic, and lipid parameters in a subpopulation of insulin-resistant subjects, as determined by the

homeostatic model assessment (HOMA), achieved with a range of doses of BMS-298585 alone and BMS-298585 20 mg in combination with 40 mg pravastatin.

- To assess the short-term safety and tolerability of a range of doses of BMS-298585 alone and 20 mg BMS-298585 in combination with 40 mg pravastatin.

METHODOLOGY: This was a multi-center, randomized, double-blind, dose-ranging, placebo-controlled trial designed to assess the safety and TG-lowering efficacy of BMS-298585, alone and in combination with pravastatin, versus placebo in subjects with mean serum TG of > 150 mg/dL and ≤ 600 mg/dL and a mean serum LDL-C level of > 130 mg/dL despite a lipid-lowering diet.

Single-blind Lead-in Phase (Period A): Period A was a 4-week dietary and placebo lead-in phase. During a screening period, subjects received dietary counseling on the NCEP Step I diet by a Registered Dietitian and were withdrawn from all lipid-lowering treatments, as necessary. Subjects with mixed dyslipidemia entered into a 4-week lead-in phase with instructions to take study medication (single-blind placebo) once daily. Subjects were to have adhered to the NCEP Step I diet for at least 4 weeks and to have been withdrawn from lipid-lowering treatments for at least 6 weeks prior to the first qualifying lipid measurement (Week 2 of lead-in phase). At the end of the lead-in phase, subjects with mean levels of serum TG (> 150 mg/dL and ≤ 600 mg/dL) and LDL-C (> 130 mg/dL) at the two qualifying visits were randomized to double-blind study treatment.

Short-term, Double-blind Phase (Period B): Period B was a randomized, double-blind treatment phase of 6 weeks duration. Eligible subjects were randomized to one of five treatment arms in a 1:1:1:1:1 ratio: BMS-298585 5 mg, BMS-298585 10 mg, BMS-298585 20 mg, BMS-298585 20 mg and pravastatin 40 mg, or placebo. Subjects were to take double-blind medication once daily for 6 weeks and to adhere to the NCEP Step I diet throughout this phase. Efficacy and safety assessments were made at specified time points.

Long-term, Double-blind Phase (Period C): Period C is an ongoing, double-blind treatment phase for all subjects who completed 6 weeks of short-term, double-blind therapy. The results of this study phase will be reported after its completion.

NUMBER OF SUBJECTS: A total of 608 subjects was enrolled in the placebo lead-in phase, of whom 321 were randomized to double-blind study medication (of which one subject was never treated) and 278 subjects completed 6 weeks of double-blind treatment.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Non-diabetic subjects between the ages of 18 and 70 years with a diagnosis of mixed dyslipidemia were eligible. Subjects had to meet additional inclusion criteria of being willing to discontinue all lipid-lowering medications and to have a fasting TG level of > 150 mg/dL and ≤ 600 mg/dL and a LDL-C level of > 130 mg/dL. To be eligible for randomization, subjects were to have a fasting TG level of > 150 mg/dL and ≤ 600 mg/dL and a LDL-C level of > 130 mg/dL as the average of two qualifying visits during the lead-in phase while off lipid-lowering medications and on a stable cholesterol-lowering diet.

TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, PRODUCT BATCH NUMBERS and DURATION OF TREATMENT: 4 week placebo lead-in phase followed by 6 weeks of oral administration: BMS-298585 5 mg (1M41363), BMS-298585 15 mg (1M41365), Pravastatin 40 mg (B5490)

REFERENCE THERAPY, DOSE, MODE OF ADMINISTRATION, PRODUCT BATCH NUMBERS and DURATION OF TREATMENT: 6 weeks of oral administration: Matching placebo for BMS-298585 (B4322A), Matching placebo for pravastatin (B4634).

CRITERIA FOR EVALUATION: Efficacy outcomes were evaluated using multiple lipid and glycemic control parameters, as well as blood pressure and body weight. The safety outcome was assessed by adverse events and laboratory parameters.

Efficacy: The primary efficacy endpoint was the mean percent change from baseline to Week 5/6 in the average fasting TG level.

Secondary efficacy outcome measures for the short-term, double-blind phase (according to the protocol) included:

- Percent changes from baseline at Week 5/6 in HDL-C, LDL-C, non-HDL-C, and TC.
- Percent changes from baseline to Week 6 in $ApoA_1$, ApoB, and fasting FFA levels.
- Changes from baseline to Week 6 in HbA_{1c}, FPG, fasting insulin, and fructosamine.
- Changes from baseline to Week 6 in metabolic surrogate markers, high-sensitivity C-reactive protein (hs-CRP) and plasminogen activator inhibitor-1 (PAI-1).
- Changes from baseline to Week 6 in SBP, DBP, body weight, BMI, and the short form-36 (SF-36) health assessment.

In addition the following outcome was also assessed:

- Changes in fasting insulin, glycemic, and lipid parameters at Week 6 in a subpopulation of insulin-resistant subjects, as determined by the homeostatic model assessment (HOMA), achieved with a range of doses of BMS-298585 alone and BMS-298585 20 mg in combination with 40 mg pravastatin.

Safety: Safety was evaluated by medical history, physical examinations, laboratory analyses, and assessment of adverse events throughout the study.

STATISTICAL METHODS: The primary efficacy outcome is the mean percent change from baseline to the average TG level at Week 5/6. Assuming a monotonic dose-response relationship, i.e., 20 mg BMS-298585 is at least as effective as 10 mg BMS-298585, and 10 mg BMS-298585 is at least as effective as 5 mg BMS-298585 with 60 evaluable subjects per dose group, at least 86% power was determined for the detection of a difference in mean percent change from baseline TG of 20%. This assumes a standard deviation of 30% and the use of a two-sided Koch-Gansky sequential testing procedure with the three dose groups and a placebo control. The overall Type I error is controlled at a 0.05 level. The primary data set is All Randomized Subjects consisting of those randomized subjects who received at least one dose of short-term, double-blind study treatment.

STUDY POPULATION: Baseline demographic and disease characteristics, summarized in the following table, were generally similar among the treatment groups.

Demographic and Baseline Characteristics

Characteristic	Placebo (N=63)	BMS-298585 5 mg (N=64)	BMS-298585 10 mg (N=61)	BMS-298585 20 mg (N=66)	BMS-298585 20 mg and Prava 40 mg (N=66)
Age, years					
Mean (SD)	52.92 (9.01)	54.41 (10.17)	54.38 (8.03)	52.11 (9.14)	54.80 (8.86)
Median	53.00	55.50	54.00	54.00	56.00
Range	27.00 - 69.00	30.00 - 70.00	27.00 - 70.00	31.00 - 70.00	27.00 - 70.00
Sex, n (%)					
Male	32 (51%)	30 (47%)	28 (46%)	33 (50%)	36 (55%)
Female	31 (49%)	34 (53%)	33 (54%)	33 (50%)	30 (45%)
Race, n (%)					
White	60 (95%)	63 (98%)	60 (98%)	65 (98%)	62 (94%)
Black	0 (0%)	1 (2%)	0 (0%)	0 (0%)	2 (3%)
Asian	1 (2%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Other	2 (3%)	0 (0%)	1 (2%)	0 (0%)	2 (3%)
BMI (kg/m^2)					
≤25	4 (6%)	7 (11%)	8 (13%)	10 (15%)	13 (20%)
>25 - ≤30	28 (44%)	26 (41%)	26 (43%)	29 (44%)	28 (42%)
>30	31 (49%)	31 (48%)	27 (44%)	27 (41%)	25 (38%)
TG (mg/dL)					
Mean (SD)	274.0 (79.71)	258.9 (80.08)	259.4 (93.49)	258.6 (79.24)	277.0 (89.58)
Median	259.0	249.3	221.5	234.3	245.8
Range	167.5 - 461.0	134.0 - 452.0	150.5 - 552.0	157.5 - 529.5	145.5 - 502.0
LDL-C (mg/dL)					
Mean (SD)	168.9 (29.27)	171.3 (27.78)	176.8 (29.02)	172.0 (30.45)	172.4 (33.30)
Median	174.0	170.3	175.5	165.8	168.0
Range	96.50 - 235.0	124.5 - 234.0	135.0 - 320.0	120.0 - 255.5	120.5 - 289.5

Data Set: All Randomized Subjects

A total of 278 of the 320 randomized subjects who received at least one dose of study medication completed the 6-week double-blind phase. The disposition of all randomized subjects is shown below.

Disposition	Placebo	BMS-298585 5 mg	BMS-298585 10 mg	BMS-298585 20 mg	BMS-298585 20 mg and Prava 40 mg
Randomized (Including Not Treated Subjects)	64	64	61	66	66
Treated[a]	63	64	61	66	66
Completed	58	57	54	54	55
Discontinued	5	7	7	12	11
- AE[b]	2	4	4	8	7
-All Others combined	3	3	3	4	4

Data Set: All Randomized Subjects

a All subjects were treated with the study treatment to which they had been randomized.

b collected on the Subject Status page of the case report form for the short-term, double-blind phase.

EFFICACY RESULTS: BMS 298585 20 mg, 10 mg, and 5 mg strengths resulted in statistically significant, dose-dependent lowering of fasting TG at Week 5/6 versus placebo ($p<0.0001$ for each pairwise comparison with placebo). The adjusted mean percent changes from baseline to Week 5/6 in fasting TG are summarized in the table below.

Primary Efficacy Analysis: Percent Change from Baseline to Week 5/6 in Fasting TG

Fasting TG Level (mg/dL)	Placebo (N=63)	BMS-298585 5 mg (N=64)	BMS-298585 10 mg (N=61)	BMS-298585 20 mg (N=66)	BMS-298585 20 mg and Prava 40 mg (N=66)
n	58	58	55	55	56
Baseline Mean (SD)	274.03 (81.25)	260.05 (80.67)	264.85 (95.78)	250.67 (71.25)	280.02 (94.79)
Adjusted Mean % Change from BL (SE)	1.09 (3.84)	-20.89 (3.00)	-32.43 (2.63)	-39.57 (2.36)	-54.67 (1.75)
95% two-sided CI	(-6.19, 8.95)	(-26.59, -14.75)	(-37.43, -27.05)	(-44.04, -34.74)	(-58.00, -51.08)
Difference in Adjusted % Change from BL vs Placebo: Mean (SE)		-21.75 (4.21)	-33.17 (3.64)	-40.22 (3.26)	
p-value		<0.0001*	<0.0001*	<0.0001*	
95% two-sided CI		(-29.61, -13.01)	(-39.96, -25.60)	(-46.32, -33.44)	

Data Set: All Randomized Subjects

* p-value < 0.0001 for each dose of BMS 298585 vs. placebo, Koch-Gansky sequential test.

After 6 weeks of treatment, all three dosage strengths of BMS-298585 were effective in raising HDL-C, and lowering non-HDL-C, and ApoB concentrations, and BMS-298585 doses of 10 mg and 20 mg also lowered LDL-C and TC levels, as shown in the table below.

Secondary Efficacy Analyses: Percent Changes from Baseline to Week 5/6 in Serum Lipid or Lipoprotein Levels

		BMS-298585			
Lipid Measurement (mg/dL)	**Placebo (N=63)**	**5 mg (N=64)**	**10 mg (N=61)**	**20 mg (N=66)**	**20 mg and Prava 40 mg (N=66)**
HDL-C n	59	58	55	55	56
Baseline Mean (SD)	45.36 (9.17)	45.15 (9.04)	47.67 (9.19)	46.65 (11.10)	44.76 (8.36)
Adjusted Mean % Change from BL (SE)	1.14 (1.90)	10.78 (2.10)	15.05 (2.25)	12.83 (2.20)	31.19 (2.54)
95% two-sided CI	(-2.55, 4.96)	(6.71, 15.00)	(10.70, 19.57)	(8.58, 17.25)	(26.28, 36.28)
LDL-C n	59	58	55	55	56
Baseline Mean (SD)	167.89 (29.46)	171.30 (27.06)	177.10 (30.01)	174.37 (29.62)	169.96 (31.36)
Adjusted Mean % Change from BL (SE)	-3.47 (2.11)	1.11 (2.20)	-7.20 (2.12)	-13.16 (1.95)	-32.10 (1.51)
95% two-sided CI	(-7.53, 0.77)	(-3.14, 5.54)	(-11.28, -2.93)	(-16.92, -9.23)	(-35.01, -29.06)
ApoB n	49	49	47	47	46
Baseline Mean (SD)	150.06 (32.86)	139.80 (21.89)	149.23 (27.74)	144.26 (27.42)	148.26 (24.66)
Adjusted Mean % Change from BL (SE)	-1.43 (2.25)	-6.06 (2.16)	-15.77 (1.96)	-22.16 (1.81)	-37.22 (1.48)
95% two-sided CI	(-5.77, 3.11)	(-10.21, -1.71)	(-19.56, -11.81)	(-25.65, -18.50)	(-40.07, -34.24)
non-HDL-C n	59	58	55	55	56
Baseline Mean (SD)	220.13 (34.13)	219.12 (31.57)	225.76 (38.45)	220.53 (36.40)	222.04 (35.61)
Adjusted Mean % Change from BL (SE)	-2.21 (1.86)	-4.11 (1.84)	-12.06 (1.73)	-17.26 (1.63)	-37.26 (1.22)
95% two-sided CI	(-5.79, 1.51)	(-7.66, -0.43)	(-15.40, -8.59)	(-20.40, -14.00)	(-39.62, -34.81)

Lipid Measurement (mg/dL)	Placebo (N=63)	BMS-298585 5 mg (N=64)	BMS-298585 10 mg (N=61)	BMS-298585 20 mg (N=66)	BMS-298585 20 mg and Prava 40 mg (N=66)
TC n	59	58	55	55	56
Baseline Mean (SD)	265.49 (35.42)	264.27 (31.14)	273.44 (39.52)	267.17 (37.27)	266.79 (37.19)
Adjusted Mean % Change from BL (SE)	-1.53 (1.37)	-1.37 (1.38)	-7.40 (1.35)	-11.37 (1.27)	-25.25 (1.06)
95% two-sided CI	(-4.19, 1.20)	(-4.06, 1.40)	(-10.02, -4.71)	(-13.85, -8.83)	(-27.31, -23.12)

Data Set: All Randomized Subjects

The combination of BMS-298585 20 mg/pravastatin 40 mg increased HDL-C, and decreased fasting TG, LDL-C, non-HDL-C, ApoB, and TC levels at Week 5/6 (Week 6 for apoB). The estimated difference in adjusted mean percent change from baseline to Week 5/6 in fasting TG between the BMS-298585 plus pravastatin group and BMS-298585 20 mg group was -25.0% (95% CI: -32.71% to -16.39%).

In addition to its effects on the lipid and lipoprotein profile of nondiabetic subjects with mixed dyslipidemia, dose-dependent reductions in FPG, fasting insulin, and blood pressures were seen after 6 weeks of treatment with BMS-298585. BMS-298585 also generally lowered HOMA-IR scores relative to baseline determinations. The table below summarizes the adjusted mean changes from baseline in FPG, fasting insulin, SBP, and DBP at Week 6.

Changes from Baseline at Week 6 in FPG, Fasting Insulin, and Blood Pressure

Secondary Efficacy Endpoint	Placebo (N=63)	BMS-298585 5 mg (N=64)	BMS-298585 10 mg (N=61)	BMS-298585 20 mg (N=66)	BMS-298585 20 mg and Prava 40 mg (N=66)
FPG (mg/dL) n	45	48	46	49	48
Baseline Mean (SD)	98.29 (12.74)	96.42 (10.46)	96.11 (8.98)	96.61 (10.33)	95.56 (12.16)
Adjusted Mean Change from BL (SE)	0.63 (1.28)	-5.13 (1.24)	-7.27 (1.27)	-8.82 (1.23)	-7.23 (1.24)
95% two-sided CI	(-1.90, 3.16)	(-7.58, -2.69)	(-9.77, -4.77)	(-11.24, -6.40)	(-9.68, -4.78)
Fasting Insulin (µU/mL) n	48	49	46	46	41
Baseline Mean (SD)	20.63 (41.29)	13.51 (9.63)	13.04 (7.79)	11.43 (7.63)	10.90 (4.75)
Adjusted Mean Change from BL (SE)	0.71 (1.39)	-2.67 (1.36)	-4.60 (1.40)	-4.69 (1.40)	-4.18 (1.49)
95% two-sided CI	(-2.02, 3.44)	(-5.34, 0.01)	(-7.36, -1.84)	(-7.45, -1.93)	(-7.10, -1.25)
SBP (mm Hg) n	55	55	50	52	56
Baseline Mean (SD)	124.47 (14.32)	123.32 (10.32)	123.84 (11.82)	122.11 (8.70)	124.03 (13.37)
Adjusted Mean Change from BL (SE)	0.15 (1.27)	-0.82 (1.27)	-2.27 (1.33)	-3.25 (1.31)	-3.44 (1.26)
95% two-sided CI	(-2.35, 2.65)	(-3.32, 1.68)	(-4.90, 0.35)	(-5.82, -0.67)	(-5.92, -0.97)

DBP (mm Hg)	n	55	55	50	52	56
Baseline Mean (SD)		78.13 (8.66)	78.24 (7.89)	77.90 (7.63)	78.27 (7.78)	78.76 (7.07)
Adjusted Mean Change from BL (SE)		-0.03 (0.81)	-0.97 (0.81)	-2.09 (0.85)	-4.02 (0.83)	-2.67 (0.80)
95% two-sided CI		(-1.62, 1.57)	(-2.56, 0.63)	(-3.76, -0.42)	(-5.67, -2.38)	(-4.25, -1.08)

Data Set: All Randomized Subjects

No consistent trends in $ApoA_1$, HbA_{1c}, or fructosamine levels were seen following 6 weeks of BMS-298585 treatment in this nondiabetic population. The drug did lower fasting FFA levels in an apparent dose-related manner, with adjusted mean percent changes from baseline to Week 6 of -37.4% and -33.1% in the BMS-298585 20 mg and BMS-298585/pravastatin combination groups, respectively.

Short-term treatment with BMS-298585 resulted in modest, dose-related increases in body weight and BMI. The adjusted mean change in body weight over the 6-week treatment period was 1.1 kg in the BMS-298585 20 mg group and 1.3 kg in the BMS-298585/pravastatin combination group relative to -0.4 kg in the placebo group.

SAFETY RESULTS: The incidence of clinical AEs during the short-term, double-blind phase was higher in the BMS-298585 treatment groups and BMS-298585 20 mg/pravastatin 40 mg group relative to the placebo group.

Overview of Safety During Short-Term, Double-Blind Phase

		BMS-298585			
	Placebo (N=63)	**5 mg (N=64)**	**10 mg (N=61)**	**20 mg (N=66)**	**20 mg and Prava 40 mg (N=66)**
At least one clinical AE	34 (54.0%)	40 (62.5%)	40 (65.6%)	44 (66.7%)	49 (74.2%)
At least one related clinical AE	10 (15.9%)	18 (28.1%)	19 (31.1%)	27 (40.9%)	28 (42.4%)
Death	0	0	0	0	0
At least one SAE	0	1 (1.6%)	0	2 (3.0%)	0
Discontinuation for AE[a]	2 (3.2%)	4 (6.3%)	5 (8.2%)	9 (13.6%)	8 (12.1%)

Data Set: All Treated Subjects

[a] As collected on Adverse Event page(s) of case report form for short-term, double-blind phase.

Edema-related events were the most frequent clinical AE. The incidence of edema-related AEs was dose-related, with respective rates of 6.3%, 11.5%, and 31.8% in the BMS-298585 5 mg, 10 mg, and 20 mg groups relative to 4.8% in the placebo group and 25.8% in the BMS-298585 20 mg/pravastatin 40 mg group. For 77% of subjects with edema-related AEs, the AEs were mild in intensity. Two subjects had an edema-related event rated as severe. Eight subjects -- all in the BMS-298585 20 mg or BMS-298585/pravastatin combination group -- were withdrawn from the study prematurely as a result of an edema-related AE. Congestive heart failure or pulmonary edema were not seen in any subject during the short-term, double-blind phase.

Among the clinical AEs reported by at least 2% of subjects overall, the incidence rates for constipation, weight gain, and dyspepsia appeared to be dose-related, with the highest rates in the BMS-298585 20 mg

group (7.6%, 6.1%, and 4.5%, respectively) relative to rates of 0%, 0%, and 1.6% in the placebo group. The frequency of each of these three adverse events in the BMS-298585 20 mg and pravastatin 40 mg group was lower than that in the BMS-298585 20 mg alone group.

Serious adverse events were reported for one subject in the BMS-298585 5 mg group (coronary artery disease) and for two subjects in the BMS-298585 20 mg group (decreased neutrophils and myocardial infarction).

Twenty-eight subjects were withdrawn from the study prematurely due to AEs. The discontinuation rate for AEs appeared to be dose-related, with 3.2% of placebo subjects discontinuing for an AE relative to 6.3%, 8.2%, 13.6%, and 12.1% of subjects in the BMS-298585 5 mg, 10 mg, 20 mg, and combination groups, respectively. Edema-related AEs were the most common AEs leading to discontinuation.

Treatment with BMS-298585 was not associated with significant elevations in CK or ALT levels. No subject had an ALT level > 3 x ULN during the short-term, double-blind phase. No subject had an elevation in CK of >10 x ULN. One subject each in the placebo and BMS-298585 10 mg groups had an elevation in CK of >5 x ULN. As assessed by the investigators, there was no relationship between the occurrence of clinical AEs of muscle ache or myalgia and CK levels in this study.

BMS-298585 treatment was associated with modest, apparently dose-related reductions in hemoglobin and WBC. Maximum mean percent reductions in hemoglobin and WBC were 8.49% and 16.37%, respectively, and were seen in the BMS-298585 20 mg group. A clinical AE of anemia was reported for three subjects, all in the BMS-298585 20 mg group. Anemia did not result in treatment discontinuation in any of these three subjects. An AE of decreased WBC was reported for one subject in the BMS-298585 10 mg group; this AE occurred in conjunction with a decreased neutrophil count (that remained above 1000 cells/mm^3) and the subject was withdrawn from the study as a result of these laboratory changes.

A dose-related downward shift in ANC values occurred following short-term treatment with BMS-298585; there was one case of neutropenia (ANC <1000 cells/mm^3), which occurred after 29 days of treatment with BMS-298585 20 mg. The subject had no concomitant infection or symptoms as a result of the low ANC value. Study treatment was discontinued and the abnormal value resolved.

CONCLUSIONS: Treatment of nondiabetic subjects with mixed dyslipidemia with the dual PPARα/γ agonist BMS-298585 for 6 weeks achieved the following:

- BMS-298585 dosage strengths of 5 mg, 10 mg, and 20 mg resulted in statistically significant, dose-dependent lowering of TG versus placebo of -21.8%, -33.2%, and -40.2%, respectively.
- BMS 298585 demonstrated increases in HDL-C for all three doses.
- BMS 298585 demonstrated reductions in non-HDL-C for all three dosage strengths accompanied by reductions in LDL-C and TC for the 10 mg and 20 mg doses.
- BMS 298585 20 mg in combination with pravastatin 40 mg resulted in decreases in TG, LDL-C, and non-HDL-C and increases in HDL-C relative to placebo.
- There were dose-dependent reductions in FPG, fasting insulin, and systolic and diastolic blood pressure with BMS-298585.
- Short-term treatment with BMS-298585 was not associated with any safety issues related to elevated CK levels or liver function tests.
- Decreases were seen in the mean change from baseline analyses for both hemoglobin and WBC following BMS-298585 treatment.
- Edema-related AEs were the most common clinical AEs, and the incidence of edema-related AEs was higher in the higher dose groups: 4.8 % (placebo), 6.3% (BMS 298585 5 mg), 11.5% (BMS 298585 10 mg), 31.8 % (BMS 298585 20 mg), and 25.8% (BMS 2985985 20 and pravastatin 40 mg).

- Edema-related AEs were assessed as mild in severity for most subjects (77%) reporting these events. There were no cases of congestive heart failure or pulmonary edema in the short-term, double-blind phase.
- There was a single case of neutropenia (ANC < 1000 cells/mm^3) in the BMS 298585 20 mg treatment group that was not associated with concomitant infection.

DATE OF REPORT: 16-Jul-2004

Attachment 3.1B: CV168008 LT Synopsis

8 page(s) excluding cover page

Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient: BMS-298585		

SYNOPSIS

Clinical Study Report CV168008 - Short-Term Combined With Long-Term Phase

TITLE OF STUDY: A Randomized, Double-Blind, Dose-Ranging, Placebo-Controlled Trial to Determine the Lipid-Lowering Efficacy and Safety of Muraglitazar Alone and in Combination with Pravastatin in Subjects with Mixed Dyslipidemia

INVESTIGATORS: 50 investigators participated in the conduct of this study.

STUDY CENTERS: 50 centers in the United States screened subjects in this study.

PUBLICATIONS: None

STUDY PERIOD: Date first subject enrolled: 5-Feb-2002

Date last subject completed: 17-Jun-2004(for the short-term combined with long-term extension phase)

CLINICAL PHASE: 2b/3

OBJECTIVES: The results of the primary objective have been reported in the short-term clinical study report. Objectives of the long-term, double-blind study were:

- To assess the long-term efficacy of a range of doses of muraglitazar and of placebo with changes in serum TG, TC, HDL-C, LDL-C, non-HDL-C, $apoA_1$, apoB, FFA, SBP, DBP, BMI, body weight, HbA_{1c}, FPG, fasting insulin, and fructosamine.
- To assess at the end of the long-term extension phase the incidence of coronary events (myocardial infarction, coronary revascularization, coronary artery disease, and coronary death) and cerebrovascular disease (stroke [CVA] or transient ischemic attack [TIA]).
- To assess the long-term safety and tolerability of a range of doses of muraglitazar and of placebo after the long term extension phase.
- To assess after long-term oral administration of double-blind treatment, changes in insulin, glycemic, and lipid parameters in a subpopulation of insulin resistant subjects, as determined by the homeostatic model assessment (HOMA), achieved with a range of doses of muraglitazar alone and in combination with 40 mg pravastatin.

Other efficacy and safety objectives not listed here were included in this protocol.

METHODOLOGY: This was a multi-center, randomized, double-blind, dose-ranging, placebo-controlled trial designed to assess the safety and TG-lowering efficacy of muraglitazar, alone and in combination with pravastatin, versus placebo in subjects with mean serum TG of > 150 mg/dL and ≤ 600 mg/dL and a mean

serum LDL-C level of > 130 mg/dL despite a lipid-lowering diet. The study design included the following 3 phases:

1) **Single-blind Lead-in Phase - Period A**: Period A was a 4-week dietary and placebo lead-in phase. During a screening period, subjects received dietary counseling on the NCEP Step I diet by a Registered Dietitian and were withdrawn from all lipid-lowering treatments, as necessary. Subjects with mixed dyslipidemia entered into a 4-week lead-in phase with instructions to take study medication (single-blind placebo) once daily. Subjects were to have adhered to the NCEP Step I diet for at least 4 weeks and to have been withdrawn from lipid-lowering treatments for at least 6 weeks prior to the first qualifying lipid measurement (Week 2 of lead-in phase). At the end of the lead-in phase, subjects with mean levels of serum TG (> 150 mg/dL and ≤ 600 mg/dL) and LDL-C (> 130 mg/dL) at the two qualifying visits were randomized to double-blind study treatment.
2) **Short-term, Double-blind Phase - Period B**: Period B was a randomized, double-blind treatment phase of 6 weeks duration. Data from the short-term phase of CV168008 are available in CV168008 ST Clinical Study Report.
3) **Long-term, Double-blind Phase - Period C**: Period C was a long-term, extension phase for all subjects who completed 6 weeks of double-blind therapy. Subjects who received combination treatment (muraglitazar 20 mg + pravastatin 40 mg) during short-term were changed to 20 mg muraglitazar alone for the long-term extension (Amendment 2). Subsequently, Amendment 8 provided for the down-titration of those subjects on 20 mg of muraglitazar to 10 mg at the long-term Week 96 visit timepoint. Subjects who did not achieve adequate LDL-C control during the long-term phase were eligible to receive adjunctive open-label lipid-lowering medication. If clinically indicated, a fibrate could be initiated, although fibrate use was prohibited for subjects receiving statin therapy. Subjects could not take a statin and fibrate in combination with study drug at any time during the study.

NUMBER OF STUDY SITES/SUBJECTS: A total of 47 sites in the United States enrolled 619 subjects. Of these 619 subjects, 11 were not included in the report for the short-term phase (CV168008 ST). These were subjects who took at least 1 dose of placebo lead-in medication; however, these subjects discontinued from the lead-in phase and never went into the short-term, double-blind phase. The documented enrollment of these subjects was received by BMS after the Case Report Form [CRF] lock of the short-term database, and their number was not included in the short-term report. None of these subjects received active study medication. Of the 321 subjects who were randomized into the short-term 6-week phase, 278 subjects completed it and 243 enrolled into the long-term phase.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Non-diabetic subjects 18 to 70 years with a diagnosis of mixed dyslipidemia were eligible. Subjects had to be willing to discontinue all lipid-lowering medications. To be eligible for randomization, subjects were to have a fasting TG level of > 150 mg/dL and ≤ 600 mg/dL and a LDL-C level of > 130 mg/dL as the average of two qualifying visits during the lead-in phase while off lipid-lowering medications and on a stable cholesterol-lowering diet.

TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, BATCH NUMBERS and DURATION OF TREATMENT: Oral administration muraglitazar 5 mg (Product Batch Number 1M41363), muraglitazar 15 mg (Product Batch Number IM41365), and pravastatin 40 mg (Product Batch Number B4634). Lead-in phase of 4 weeks, 6-week double-blind treatment phase, and 100-week, double-blind, long-term extension phase.

REFERENCE THERAPY, DOSE, MODE OF ADMINISTRATION, BATCH NUMBERS and DURATION OF TREATMENT: Matching placebo for muraglitazar (Product Batch Number B4322A) and matching placebo for pravastatin (Product Batch Number B4634). Lead-in phase of 4 weeks, 6-week double-blind treatment phase, and 100-week, double-blind, long-term extension phase.

CRITERIA FOR EVALUATION: The following were the efficacy and safety endpoints for the short-term combined with long-term phase:

- Percent changes from baseline in fasting TG, TC, LDL-C, HDL-C, non-HDL-C, $apoA_1$, apoB, and FFA levels to the end of long-term extension.
- Changes from baseline in SBP, DBP, body weight, BMI, waist circumference, and health assessment to the end of the long-term extension.
- Changes from baseline in HbA_{1c}, FPG, fructosamine, and fasting insulin to the end of the long-term extension.
- Changes from baseline in metabolic surrogate markers hs-CRP and PAI-1 to the end of the long-term extension.
- Frequencies of coronary events (myocardial infarction, coronary revascularization, coronary artery disease, and coronary death) and cerebrovascular events (stroke [CVA] and transient ischemic attack [TIA]) through the end of the study.

Safety outcomes were assessed by evaluation of adverse events, laboratory values, and vital sign and ECG measurements as well as proactive collection of edema-related events.

STATISTICAL METHODS: Efficacy analyses consisted in providing summary statistics on the change or percent change from baseline in all efficacy variables at different timepoints by treatment group. Summary statistics consisted of mean, standard deviation, 95% Confidence Interval, quartiles, and range. They were presented by treatment group and by timepoint. No formal statistical testing between treatment regimens generating p-values was performed. The evaluation of drug safety included the reporting of AEs and laboratory abnormalities collected during the short-term combined with long-term phase. No statistical tests were performed to compare safety variables between the treatment groups.

STUDY POPULATION: Non-diabetic subjects with mixed dyslipidemia made up the study population. A total of 243 randomized subjects completed the short-term phase and received at least 1 dose of study medication during the long-term phase. Baseline demographic characteristics for the subjects who entered the long-term phase are summarized in the following table. Demographic characteristics were generally similar across the 5 treatment groups.

Subject Demographics and Baseline Characteristics

Characteristic	MUR 5 N=51	MUR 10 N=52	MUR 20 N=42	MUR 20 +PRA N=49	PLACEBO N=49	Total N=243
Age, years						
Mean (SD)	54.5 (10.0)	54.4 (8.2)	51.5 (9.0)	54.8 (8.7)	53.1 (9.3)	53.7 (9.1)
Gender						
Male	23 (45.1%)	24 (46.2%)	21 (50.0%)	30 (61.2%)	27 (55.1%)	125 (51.4%)
Female	28 (54.9%)	28 (53.8%)	21 (50.0%)	19 (38.8%)	22 (44.9%)	118 (48.6%)
Race						
White	50 (98.0%)	51 (98.1%)	42 (100.0%)	46 (93.9%)	48 (98.0%)	237 (97.5%)
Black or African American	1 (2.0%)	0 (0%)	0 (0%)	2 (4.1%)	0 (0%)	3 (1.2%)
Other	0 (0%)	1 (1.9%)	0 (0%)	1 (2.0%)	1 (2.0%)	3 (1.2%)
Ethnicity						
Hispanic/ Latino	1 (2.0%)	1 (1.9%)	0 (0%)	4 (8.2%)	5 (10.2%)	11 (4.5%)
Non Hispanic/ Latino	50 (98.0%)	51 (98.1%)	42 (100.0%)	45 (91.8%)	44 (89.8%)	232 (95.5%)
Body Mass Index, kg/m^2						
Mean (SD)	30.3 (4.5)	30.0 (4.7)	29.2 (4.0)	29.5 (4.0)	30.6 (4.8)	29.9 (4.4)
TG, mg/dL						
Mean (SD)	265.3 (78.6)	265.3 (98.0)	242.5 (71.0)	276.4 (89.7)	269.7 (80.7)	264.5 (84.6)
HDL-C, mg/dL						
Mean (SD)	44.5 (7.9)	47.9 (9.3)	48.2 (11.8)	44.4 (8.2)	45.4 (9.1)	46.0 (9.3)

Dataset: Subjects Who Entered the Long-Term Phase

A total of 134 completed the long-term phase of the study. The most frequent reason for premature discontinuation was the occurrence of an adverse event (AE) and the second most frequent reason was withdrawal of consent. The disposition of all subjects who entered the long-term phase is shown below.

Disposition of All Subjects Who Entered the Long-Term Phase and Primary Reason for Discontinuation

Disposition	MUR 5	MUR 10	MUR 20	MUR 20 + PRA	PLACEBO	Total
Total Who Entered Long-Term Phase	51	52	42	49	49	243
Completed Long-Term Phase	29	32	20	23	30	134
Premature Discontinuation of Long-Term Phase	22	20	22	26	19	109
Primary Reason for Premature Discontinuation						
Adverse Event	10	6	14	16	3	49
Subject Withdrew Consent	7	8	7	5	7	34
Lost to Follow-up	2	1	1	2	4	10
Other	1	3	0	0	2	6
Treatment Failure/Lack of Efficacy	0	1	0	2	2	5
Non-compliance	2	1	0	0	0	3
Death	0	0	0	1	0	1
Subject No Longer Meets Study Criteria	0	0	0	0	1	1

Dataset: Subjects Who Entered the Long-term Phase
Adverse events as recorded on the CRF status page for the Long-Term Double-Blind Phase

EFFICACY RESULTS: It should be noted that a similarly high percentage of subjects in each of the dose groups (approximately 54%) started lipid-lowering medication. For this reason, although the lipid profile improved over time, the difference among the treatment groups remained constant. Since subjects were permitted to take lipid-lowering medication, the efficacy analyses were restricted to the results of the TG, HDL-C, apoB, and FFA variables. No formal statistical testing between treatment regimens generating p-values was performed. Amendment 2 provided that the scheduled treatment for those subjects who completed 6 weeks of double-blind treatment on a daily dosage of muraglitazar 20 mg/pravastatin 40 mg were changed from that combination therapy to muraglitazar 20 mg alone for the long-term phase of the study. That amendment also added provisions for adjunct treatment with open-label lipid-lowering medications in the long-term, extension phase for subjects who did not achieve adequate LDL-cholesterol control. Amendment 8 provided for the down-titration of the muraglitazar 20-mg dose to 10 mg at the long-term Week 96 visit timepoint.

Meaningful changes were apparent in all 4 lipid parameters under study, and the impact on the lipid parameters seen in the short-term (ST) phase in the muraglitazar-treated groups was maintained throughout the long-term phase. The reduction in serum TG seen in the ST phase in the muraglitazar-treated groups was maintained through Week 106 of the short-term combined with long-term phase at the 5 mg and 10 mg dosage. The increase in HDL-C seen in the ST phase was generally observed throughout the long-term phase, especially at the 5 mg dose. Reductions from baseline values in apoB at Week 6 were also observed in the long-term phase, and were either sustained or further reduced across all treatment groups at the Week

106 timepoint. There were also decreases in FFA levels in the muraglitazar-treated groups. For all 4 lipid parameters, some change from baseline was also seen in the placebo group (all treatment groups were permitted to add lipid-lowering medications after the short-term phase [Amendment 2]).

The table below summarizes the results of the lipid profile variables analyzed in this report. Geometric mean percent changes from baseline in the 4 parameters are shown at Weeks 5/6 (or Week 6, whichever is applicable) and 106 of the short-term combined with long-term phase

Percent Changes from Baseline for Selected Timepoints During the Short-Term Combined with Long-Term Phase

	MUR 5 N=51	MUR 10 N=52	MUR 20 N=42	MUR 20 + PRA N=49	PLACEBO N=49
			Fasting TG (mg/dL)		
Week 5/6	n=51 -20.0	n=52 -32.3	n=42 -41.1	n=49 -55.9	n=49 -0.5
Week 106	n=28 -41.4	n=31 -42.9	n=20 -54.9	n=23 -55.0	n=29 -17.0
			HDL-Cholesterol (HDL-C) (mg/dL)		
Week 5/6	n=51 10.72	n=52 14.47	n=42 15.01	n=49 33.10	n=49 2.35
Week 106	n=28 22.66	n=31 19.66	n=20 28.85	n=23 34.64	n=29 11.43
			Apolipoprotein B (mg/dL)		
Week 6	n=47 -4.9	n=49 -16.1	n=40 -24.7	n=45 -38.0	n=47 -1.9
Week 106	n=27 -28.0	n=29 -29.0	n=19 *	n=21 -36.0	n=28 -19.7
			Fasting FFA (mEq/L)		
Week 6	n=47 -25.3	n=49 -35.5	n=41 -37.9	n=43 -34.8	n=46 -1.7
Week 106	n=27 -21.6	n=29 -20.0	n=20 -18.9	n=20 -17.2	n=29 3.1

*no value was reported for this timepoint, since there were fewer than 20 subjects in this treatment group with available data at both baseline and Week 106 for apoB

SAFETY RESULTS: The incidence of adverse events across the 5 treatment groups was generally similiar. The most frequently reported AE was peripheral edema which occurred across all treatment groups; however, the incidence of peripheral edema was most similiar in the muraglitazar 10 mg, 20 mg, and 20 mg + pravastatin groups. Increased weight was the second most frequent event and was reported in all 5 treatment groups, although the smallest increases were seen in the muraglitazar 20 mg + pravastatin and the placebo arms.

The rates of SAEs were similar in all treatment groups except for the muraglitazar 20 mg group, which had only 1 SAE. A total of 22 subjects reported SAEs in the short-term combined with long-term phase. The muraglitazar 5 mg and the placebo groups had similiar numbers of serious adverse events. The muraglitazar 5 mg and muraglitazar 10 mg groups had 10 and 6 discontinuations due to AEs, respectively, and the placebo group had 3 discontinuations due to AEs. In the 2 highest-dose muraglitazar groups, there was a range of 13 to 16 subjects with discontinuations due to AEs. The incidence of adverse drug reactions (ADRs) was comparable across the 5 treatment groups. The table below presents a summary of AEs by treatment group.

Summary of Adverse Events by Treatment Group

Event	Number (%) of Subjects				
	MUR 5 N=51	**MUR 10 N=52**	**MUR 20 N=42**	**MUR 20 + PRA N=49**	**PLACEBO N=49**
At least 1 AE	51 (100)	50 (96.2)	42 (100)	48 (98.0)	45 (91.8)
At least 1 SAE	5 (9.8)	6 (11.5)	1 (2.4)	4 (8.2)	6 (12.2)
At least 1 adverse drug reaction	29 (56.9)	36 (69.2)	27 (64.3)	33 (67.3)	25 (51.0)
Death	0	0	0	1 (2.0)	0
Discontinuations due to AE	10 (19.6)	6 (11.5)	13 (31.0)	16 (32.7)	3 (6.1)

Dataset: Subjects Who Entered the Long-term Phase
N= Number of subjects who entered the long-term phase
Non=-serious events up to 30 days post short-term combined with long-term included
Serious events up to 30 days post short-term combined with long-term phase included
Adverse drug reaction includes events with a relationship to study drug of: certain, probable, possible, and missing
Discontinuations due to AE includes all events requiring action taken regarding study drug (5=Discontinued study drug)

All edema-related events were either mild or moderate in intensity. No subjects in the placebo treatment group discontinued due to edema-related adverse events. In both the muraglitazar 5 mg and the muraglitazar 10 mg groups, 1 subject in each group discontinued for edema-related events.

One subject in the muraglitazar 20 mg treatment group was reported to have congestive heart failure (CHF) of mild intensity. The subject was a 53-year old obese white female with a history of smoking and dyslipidemia. She gained a total of 12.7 kg between screening and study day 85 and was discontinued for edema and weight gain. Eight days after discontinuing study medication, the subject had worsening edema and shortness of breath and the investigator reported CHF (mild intensity). The subject received outpatient treatment with furosemide and the event resolved in 9 days.

There were 27 subjects reporting events of myalgia: 7 subjects in the muraglitazar 5 mg group, 8 subjects each in the muraglitazar 10 mg and 20 mg groups, 2 in the muraglitazar 20 mg + pravastatin group, and 2 in the placebo group. A total of 13 subjects (5.3%) reported myalgia events while on statins in all treatment groups with the exception of the muraglitazar 20 mg + pravastatin group, which reported none.

A total of 6 subjects had CK values greater than 5 times the upper limit of normal (ULN) in 4 of the 5 treatment groups. A CK value greater than 10 times the ULN occurred in 2 subjects, 1 in the muraglitazar 5 mg group and 1 in the muraglitazar 10 mg group. There were 2 subjects with alanine

aminotransferase (ALT) values greater than 5 times ULN, both of whom were in the muraglitazar 10 mg group; no subject was found to have elevated ALT values > 3 times ULN in combination with a total bilirubin> 2 mg/dL.

CONCLUSIONS: The results of the short-term combined with long-term phase of this double-blind, placebo-controlled, dose-ranging study in 243 subjects demonstrate that muraglitazar at doses of 5 mg and 10 mg, administered once daily was well-tolerated, safe, and effective in improving lipid profiles and maintaining those improvements for the duration of the long-term phase in non-diabetic subjects with mixed dyslipidemia.

The results supporting these conclusions were as follows:

Efficacy

- decreases from baseline in TG were observed in subjects on a muraglitazar treatment by Week 6, and were sustained or continued to improve throughout the long-term extension of the study relative to subjects in the placebo treatment group
- increases from baseline in HDL-C were seen in subjects on a muraglitazar treatment by Week 6 and were sustained throughout the long-term extension of the study relative to subjects in the placebo treatment group
- decreases from baseline in apoB were observed in subjects on a muraglitazar treatment by Week 6 and continued throughout the long-term extension of the study relative to subjects in the placebo treatment group
- decreases from baseline in FFA were observed in subjects on a muraglitazar treatment by Week 6, and values remained decreased from baseline throughout the long-term extension of the study relative to subjects in the placebo treatment group

Safety

- there was no signal for liver or muscle toxicity
- there was 1 death during the study secondary to a motor vehicle accident (in which the subject was a passenger), judged by the investigator to be not related to study drug
- there was 1 case of CHF (in the muraglitazar 20 mg group) reported by the investigators; this was judged to be mild and resolved in 10 days
- all edema-related events were either mild or moderate and occurred more frequently in the subjects on a muraglitazar treatment, compared with subjects on placebo treatment; 18 subjects discontinued due to edema-related events with 16 of the subjects in the 2 muraglitazar 20 mg groups
- modest decreases in hemoglobin, WBC, and neutrophil values were observed in subjects who received muraglitazar, compared with subjects on placebo treatment

Overall, the lipid effect and the positive safety profile seen at the end of the short-term phase was durable when muraglitazar was administered for up to 106 weeks to non-diabetic subjects with mixed dyslipidemia.

DATE OF REPORT: 22-Oct-2004

Attachment 4.2: Expert Commentary

6 page(s) excluding cover page

Mode of Action of Muraglitazar-Induced Bladder Cancer in Male Rats

Muraglitazar induced urothelial carcinomas of the urinary bladder in male rats in a two-year bioassay. No bladder tumors were induced in the female rat, although a small percentage of the female rats demonstrated hyperplasia. There was no evidence of an increased incidence of hyperplasia or malignancy of the urinary tract in male or female mice, and there was no evidence of urothelial hyperplasia in monkeys administered muraglitazar for up to a year.

Bladder cancer in rats, particularly the male, has become a common finding with many of the dual PPARα and γ agonists and with PPARγ agonists. Any mode of action for these male rat bladder tumors must be pharmacologically based. Two alternatives have been hypothesized: 1] bladder cancer is due to the direct effect of the agonist on the PPARγ present in the urothelium; or 2] an indirect effect based on pharmacological alterations in urine composition leading to the formation of urinary solids, cytotoxicity, regenerative hyperplasia, and tumors. Bristol-Myers Squibb has performed an extensive series of investigative studies to explore both of these hypotheses. The following summary is based on basic knowledge of PPAR receptors in the bladder, and the results of the various studies that have been performed by Bristol-Myers Squibb.

Muraglitazar has been negative in a battery of genotoxicity assays, thus a nongenotoxic mechanism such as increased cell proliferation, or inhibition of apoptosis is necessary to explain the carcinogenic response.

Muraglitazar is not excreted to much of an extent in the urine (< 5% of the administered dose appears in the urine, most of which is pharmacologically inactive metabolites). There are several aspects of PPARγ biology and observations produced by Bristol-Myers Squibb that strongly argue against the induction of bladder tumors as a result of direct interaction of the agonist with urothelial receptors. As they have shown, there is little difference between rats and mice with respect to transactivation of either PPARα or PPARγ with muraglitazar. Others have shown that there is little difference between male and female rats with respect to binding and transactivation of PPAR agonists at these receptors. Furthermore, the male rat-specificity of the urinary bladder tumorigenic response cannot be linked to greater drug exposures in male rats since Bristol-Myers Squibb demonstrated that systemic exposures to muraglitazar were higher in female rats and male and female mice in the oral carcinogenicity studies and that bladder tissue levels were comparable in male and female rats. Thus, activation of the receptor does not readily explain either the sex or species differences observed with muraglitazar.

The biology of PPARγ agonists on the urothelium show that these agonists inhibit urothelial proliferation, potentiate differentiation, and in neoplastic urothelium, increase apoptosis. Bristol-Myers Squibb showed that muraglitazar did not alter urothelial apoptosis in rats. In addition, extensive two-year bioassays and numerous shorter term assays have failed to demonstrate any cytotoxic, proliferative, or neoplastic effect of PPARα agonists on the rodent urothelium, suggesting urothelial PPARα is not likely

directly involved in the urinary bladder mucosal effects seen in male rats administered muraglitazar.

The alternative hypothesis to a direct effect of muraglitazar on urothelium is for a pharmacologically based indirect effect producing changes in urinary composition leading to the formation of urinary solids which act as irritants to the urothelium producing cytotoxicity, necrosis, sustained regenerative proliferation and ultimately tumors. The data produced by Bristol-Myers Squibb in several studies strongly support this hypothesis, and will only be briefly summarized here.

Extensive analyses involving a 3-month study in young and aged rats and a 21 month oral investigative time course study with interim sacrifices every 3 months beginning at 6 months of age have clearly delineated the time course of events related to muraglitazar-induced bladder tumors. The earliest event is the formation of a calcium phosphate-containing precipitate, along with aggregates of magnesium ammonium phosphate crystals, and possibly the small rod-like calcium oxalate crystals. By six months, there is the appearance of calcium phosphate crystals and by nine months, there is clear evidence of calcium phosphate calculi. A lithogenic environment was produced by administration of muraglitazar at 50 mg/kg per day, including maintenance of urinary pH at 6.5 or greater, resulting in a marked decrease in urinary citrate levels, an increase in urinary oxalate levels, and a decrease in soluble urinary calcium but an increase in total urinary calcium. Formation of urinary solids is a consequence of a complex interaction of numerous processes including calcium, magnesium, phosphate, oxalate, citrate (a chelator of calcium), and protein (qualitative and quantitative), and the entire interaction is greatly influenced physico-chemically by pH. Calcium-containing precipitates occur more readily as the pH is increased, and previous studies have demonstrated that in the rat it generally occurs in the urine when pH is $\geq$ 6.5. However, the precise threshold level for the pH effect can vary depending on the overall composition of the urine which will be reflective of the species, strain, diet, feeding cycle, and several other variables that can influence urinary composition.

The most obvious means of testing this hypothesis is to co-administer NH_4Cl in the diet to produce acidified urine. This was accomplished in the 21-month study by Bristol-Myers Squibb, although the pH was not consistently maintained below 6.5. The results are striking. Co-administration of 1% NH_4Cl prevented formation of most of the urinary solids, particularly calcium-containing crystals, including phosphate and oxalate, and calculi. This was accompanied by prevention of the cytotoxicity, necrosis, regenerative proliferation, and tumor formation as detected by evaluation of the urothelium by light microscopy and scanning electron microscopy (SEM) and by bromodeoxyuridine (BrdU) labeling index. Co-administration of NH_4Cl did not alter muraglitazar pharmacokinetics, or significantly change blood or urine concentrations.

As expected for a urine-mediated process, the changes in the urothelium were initially detected nearly exclusively in the ventral dome, where urine accumulates in the horizontally positioned rat. As the lesions progressed, the changes progressed more peripherally to include the dorsal dome and the remainder of the bladder. This is a

phenomenon frequently seen in bladder carcinogenesis and related to the mediation of carcinogenesis through the urine rather than blood.

The male rat is more likely to develop urinary solids and the proliferative responses to them. This is believed to be primarily due to the high urinary protein levels, especially α_{2u}-globulin, present in the male rat. Administration of other carcinogens that are dependent on formation of urinary calcium-containing solids, such as sodium saccharin and sodium ascorbate, do not have a significant effect in NBR male rats, a strain of rats that does not produce α_{2u}-globulin. Additional factors that favor the male rat are the more severe and earlier appearance of aging nephropathy and the longer urethra. Mice are significantly less susceptible to the formation of calcium-containing solids primarily because of the lower concentration of calcium, phosphate, and magnesium present in mouse urine compared to rat urine. For example, calcium concentration is 10-20 times greater in the rat compared to the mouse.

Rodents are more likely to form urinary solids than are dogs and primates, presumably because of the much denser urine that is normally present in rodents, 1500-3000 mosmol. compared to < 400 in humans even under conditions of dehydration.

In summary, the data that has been produced by Bristol-Myers Squibb strongly supports the hypothesis of an alteration in urinary composition leading to formation of urinary solids as the mode of action for the formation of male rat urinary bladder cancer by muraglitazar. It appears that the lithogenic milieu that is generated is primarily due to a marked decrease in citrate, with a slight increase in oxalate and maintenance of a urinary pH of 6.5 or greater. A decrease in urinary protein may contribute to this, since protein has a dual effect. At high concentration urine protein potentiates the formation of urinary solids by acting as a nidus, whereas reduced concentrations of urine protein my result in a diminished ability to counter formation of urinary solids because their binding effects to calcium.

Based on a mode of action of formation of urinary solids, a prediction of what the response in humans will be can readily be made. This has already begun to be investigated by Bristol-Myers Squibb in clinical trials. There is less likelihood of formation of urinary solids in humans than in rodents. More importantly, even if urinary solids are formed in the human, it is unlikely that this would pose a carcinogenic risk. There is no evidence that urinary precipitate or crystals have any potential for carcinogenicity in the human urothelium. Microcrystalluria of various types signals three potential effects in humans: 1] no effect; 2] an early sign of calculus formation; or 3] an indicator of systemic disease, such as urate crystals in gout. Calculi generally are also not considered to be a carcinogenic risk for humans. In contrast to the rodent, urinary calculi in humans generally will not remain for long periods of time, mostly because of the anatomic relationships of the lower urinary tract and the fact that humans are vertical, upright animals. In the rodent, urinary solids can rest in the dome of the bladder without causing complete obstruction of the lower urinary tract. In humans, many of the urinary solids are passed spontaneously or cause obstruction accompanied by severe pain leading to a visit to the urologist for their removal. Further complicating the relationship of

calculi to cancer in humans is the fact that long-standing calculi in humans are always accompanied by bacterial infection, a known risk factor for human bladder cancer itself.

To evaluate humans for this mode of action is readily achievable by utilizing screening for hematuria and crystals in routine urinalysis. Hematuria is an indicator of urinary tract toxicity and cancer; it is very sensitive albeit not very specific. Nevertheless, the American Urological Association has put forth guidelines on how to evaluate hematuria in patients. This has been accomplished in clinical trials with muraglitazar at the request of the FDA. Based on observations from the muraglitazar Phase 3 clinical program, there clearly is not a signal for bladder cancer (although one would not expect it in such a relatively short period of time or based on the mode of tumor development demonstrated in rats).

The relationship of muraglitazar treatment to the formation of urinary calculi in diabetic patients is under investigation. Whether humans have a similar lowering of citrate in response to muraglitazar treatment has yet to be determined. Regardless, even if it does, and even if urinary solids are formed in humans, it would still not predict a cancer risk in humans. If it turns out that muraglitazar enhances urinary tract calculus formation, this could readily be prevented by consumption of an acidifying agent when taking the medicine, such as cranberry juice. Since this has not been a problem with other PPARγ agonists that have been used clinically (troglitazone, pioglitazone, and rosiglitazone), it is not anticipated that calculus formation will be a consequence of muraglitazar administration.

In summary, Bristol-Myers Squibb has performed an extensive battery of mechanistic studies supporting the pharmacologically based, urinary solid hypothesis for the induction of bladder cancer in male rats, which explains the sex and species differences observed in two-year bioassays. They have also performed extensive evaluations of receptor binding and transactivation analyses, providing additional data that argue against direct effects on urothelial PPARs as a mode of action for the induction of these bladder tumors. In combination with the known anti-proliferative biology of the PPARγ agonists on the urothelium, the studies performed by Bristol-Myers Squibb, and the overall weight of the evidence, I am confident that muraglitazar does not pose a carcinogenic hazard to humans.

7/26/05

Samuel M. Cohen, MD, PhD
Professor and Chair, Pathology and Microbiology
Havlik-Wall Professor of Oncology
University of Nebraska at Omaha Medical Center

I have evaluated the preclinical data exploring the mechanism of urinary bladder tumorigenesis in male rats treated with muraglitazar and fully concur with the expert opinion rendered by Dr. Cohen

7/27/05

James A. Swenberg DVM, PhD, Diplomate ACVP
Kenan Distinguished Professor of Environmental Sciences and Engineering
Professor of Pathology and Laboratory Medicine, and Nutrition
Director, Center for Environmental Health and Susceptibility
Director, Curriculum in Toxicology
University of North Carolina at Chapel Hill

I have evaluated the preclinical data exploring the mechanism of urinary bladder tumorigenesis in male rats treated with muraglitazar and fully concur with the expert opinion rendered by Dr. Cohen.

7-27-05

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Attachment 5: Details of Clinical Pharmacology Studies

7 page(s) excluding cover page

1 DETAILS OF CLINICAL PHARMACOLOGY STUDIES

The general pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of muraglitazar have been investigated in 20 clinical pharmacology studies in the US and 2 studies in Japan. These comprised 18 studies in healthy subjects in the US and 2 in Japan, one Phase 2a PK/PD study in patients with type 2 diabetes, and one PK study in subjects with stable hepatic impairment (Table 5). In addition, population pharmacokinetic analysis results are presented from the Phase 2a study and a Phase 3 study (CV168018) in type 2 diabetic subjects.

Table 1 Outline of Clinical Pharmacology Studies of Muraglitazar

STUDY TYPE	STUDY NUMBER(S)
Safety and Pharmacokinetics in Healthy Subjects	
Single-Dose Administration	CV168001
Multiple-Dose Administration	CV168004
ADME	CV168007, CV168041
Pharmacokinetics and Pharmacodynamics in Type 2 Diabetic Subjects	
Multiple-Dose Administration	CV168002
Pharmacokinetics in Special Populations	
Age-Gender	CV168010
Single-Dose Administration in Japanese Subjects	CV168009
Multiple-Dose Administration in Japanese Subjects	CV168027
Hepatic Insufficiency	CV168040
Bioavailability Studies	
Relative Bioavailability	CV168014
Food Effect	CV168003, CV168011
Drug Interaction Studies	
Warfarin	CV168003
Pravastatin	CV168012
Glyburide	CV168013
Simvastatin	CV168015
Gemfibrozil	CV168037
Metformin	CV168039
Atorvastatin	CV168044
Fenofibrate	CV168046
Ketoconazole	CV168047
Famotidine	CV168060
Thorough ECG Evaluation	
Multiple-Dose ECG Study	CV168043

1.1 Muraglitazar General Characteristics

Muraglitazar is an oxybenzylglycine that is insoluble in water at 24 ± 3°C. The aqueous solubility increases with increasing pH which reduces the possibility of drastic reductions in oral bioavailability with co-administration of agents that increase gastric pH. In a clinical study (CV168060) an agent that increases gastric pH (famotidine) did not affect the Cmax or the AUC(INF) of muraglitazar in healthy subjects.

The final commercial formulation of muraglitazar is a non-citric acid tablet manufactured from a common dry granulation, for which clinical studies (CV168014) and in vitro dissolution assessments indicate similar bioavailability to the initial clinical formulations (solution and capsules).

1.2 Muraglitazar Pharmacokinetic Characteristics

1.2.1 Absorption

Following oral administration, muraglitazar is rapidly absorbed with peak plasma concentrations observed between 0.5 to 6 hours, with a median of 3 hours for the 5 mg dose. Absolute oral bioavailability has not been established because an intravenous formulation is not available. However, it is estimated that the oral bioavailability of muraglitazar is high as suggested by the 45% recovery of total radioactivity in bile and urine for orally administered [^{14}C] muraglitazar (assuming no intestinal metabolism). Administration with a high fat meal reduced muraglitazar Cmax by 33% with no change in overall exposure (AUC). This decrease in Cmax is considered not clinically significant.

Plasma concentrations of muraglitazar increased in a dose-proportional manner over and beyond the therapeutic dose range (up to 20 mg). During once-daily administration, steady state concentrations of muraglitazar are achieved within 7 days, in agreement with a terminal half-life of approximately 24 hours (range 19 to 31 hours). The accumulation index of muraglitazar at steady state ranges from 1.5 to 1.9. Over the therapeutic concentration range, muraglitazar is highly bound to human plasma proteins (99%), primarily albumin.

1.2.2 Metabolism

Muraglitazar is extensively metabolized through both phase 1 and phase 2 pathways. The major phase 1 biotransformation pathways are hydroxylation, O-demethylation, and isoxazole ring opening. The major phase 2 pathway is glucuronidation. In plasma, the parent compound is the major component (~76% of the drug-related exposure), with muraglitazar glucuronide, O-demethyl glucuronide muraglitazar, hydroxy-muraglitazar glucuronide, and the acetylurea derivative of muraglitazar as the prominent circulating plasma metabolites. In feces, approximately 22% of the radioactivity is represented by the parent compound, with hydroxy-muraglitazar (~24% of the dose), O-demethyl muraglitazar (~3% of the dose), O-demethyl hydroxy muraglitazar (~12% of the dose), and urea derivatives of muraglitazar (~19% of the dose) as the major fecal metabolites. The major biliary metabolites were muraglitazar glucuronide (15% of total radioactivity (TRA)), hydroxy-muraglitazar glucuronide (6% of TRA), O-demethyl-hydroxy glucuronide (7% of TRA), and O-demethyl muraglitazar (4% of TRA). Glucuronide of muraglitazar was excreted in the bile of human subjects, although none was detected in feces. The predominant metabolite identified in urine was the glucuronide (~1% of the dose).

Seven oxidative metabolites of muraglitazar have been synthesized and tested for in vitro PPARα and PPARγ binding affinity and receptor activation. None of these seven metabolites showed significant PPARα agonist functional activity. Only one metabolite, hydroxy-muraglitazar, demonstrated significant PPARγ agonist functional activity, being 5-7 fold less potent (EC_{50} value) than muraglitazar in a transactivation assay.

In vitro and in vivo, muraglitazar is a substrate for multiple cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT) enzymes. The overall oxidative metabolism of muraglitazar appears to be mediated by CYP3A4 (38%), 2C19 (35%), 2C9 (15%), 2C8 (12%), and 2D6 (0.6%) in humans. For phase 2, UGT1A3, UGT1A1, and UGT1A9 are the more prominent enzymes. Results from in vitro studies suggested that muraglitazar might be an inhibitor of CYP2C9 (IC_{50}=5.2 μM) and 2C8 (IC_{50}=7.9 μM), but an unlikely inhibitor of CYP2C19 (IC_{50}=56 μM) and CYP3A4 ($IC_{50=}$164 μM). However, results from clinical studies demonstrated no significant inhibitory effects of muraglitazar on drugs known to be substrates of CYP2C9, 2C19, or 3A4 (see below for details). Although clinical studies to address the inhibitory CYP2C8 potential have not been performed, an effect is unlikely given that the IC_{50} for CYP2C8 inhibition is 4-8 fold

higher than the Cmax with a 5 mg dose. Furthermore, few commonly used anti-diabetic or lipid-lowering agents are CYP2C8 substrates.

1.2.3 Excretion

Muraglitazar appears to be mainly excreted in the feces, with biliary elimination as the major clearance pathway. Muraglitazar is eliminated as parent compound, metabolites and conjugates. Minimal renal excretion (<4%) occurs. Accordingly, it is unlikely that renal impairment will alter the pharmacokinetics of muraglitazar.

1.3 Pharmacokinetics in Special Populations

Muraglitazar PK appear to be similar in type 2 diabetic patients and healthy subjects. Although the 5 mg muraglitazar AUC(TAU) values appeared to be slightly higher in a small sample of diabetic patients than in healthy subjects, a population PK analysis in a larger population indicated that the clearance and AUC values in diabetic patients do not differ from those seen in healthy subjects.

Muraglitazar PK is similar in males and females. In healthy elderly subjects, muraglitazar pharmacokinetics do not appear to differ significantly when compared to young healthy subjects. Although the AUC values of elderly subjects were slightly higher (26%), this difference is considered not to be clinically significant. Muraglitazar PK is similar in healthy Japanese and Caucasian subjects.

Muraglitazar PK is similar in subjects with mild hepatic impairment and healthy matched control subjects. In subjects with moderate or severe hepatic impairment, there is a 1.7 to 2.8-fold increase in AUC when compared to matched control subjects.

1.4 Multiple-Dose Pharmacokinetics of Muraglitazar in Type 2 Diabetic Subjects

After administration of multiple ascending doses of muraglitazar to type 2 diabetic patients, the median Cmax of muraglitazar generally occurred at approximately 3 hours (range 1-4 hours). On Day 1 of administration, for doses (0.25, 1.5, 5, 20, and 50 mg QD) that increased in the ratio of 1 : 6 : 20 : 80 : 200, Cmax increased in the ratio of 1 : 10 : 14 : 53 : 155, and the AUC(TAU) increased in the ratio of 1 : 9 : 20 : 63 : 178, respectively. On Day 28 of administration, Cmax increased in the ratio of 1 : 8 : 15 : 43 : 97, and

AUC(TAU) increased in the ratio of 1 : 7 : 16 : 56 : 166. These data suggest that Cmax and AUC(TAU) increased in a less than proportional manner to muraglitazar at doses ≥ 5 mg after 28 days of dosing. The accumulation index (AI) ranged from 1.5-1.9 on Days 14 and 28. Steady state appears to have been reached by Day 14. The terminal half-life of muraglitazar was approximately 26-31 hours at doses ≥ 5 mg (range 19 to 31 hours). The accumulation half-life ranged between 18-21 h, which is consistent with the terminal half-life estimates and indicates predictable, linear pharmacokinetics.

1.5 Population Pharmacokinetic Analysis

A population PK analysis performed on data obtained from 285 type 2 diabetic subjects estimated the population average clearance (CL) at approximately 1.45 L/hr, consistent with previous non-compartmental analyses of healthy subject data. The inter-subject variability (CV%) associated with muraglitazar PK ranged from 34-40%, suggesting that drug concentrations can be reliably predicted from the dose administered.

None of the patient covariates explored, including age, race, and gender, appeared to have an impact on the CL of muraglitazar. The subjects with greater body weight have a greater estimated volume of distribution of the central compartment (V_c). However, it was concluded that none of the covariates tested would require dosage adjustments.

In this population PK analysis there was an apparent inverse relationship between HbA_{1c} at 24 weeks and drug exposure across the 2.5 and 5 mg dose groups data from subjects in the Phase 3 study CV168018). Although there was a greater incidence of edema in the 5 mg vs the 5 mg dose group, there was no relationship between muraglitazar exposure and edema within each of the 2 doses. From these limited data, it appears that subjects with edema did not have exposures which were different than those without edema receiving the same dose. However, since few subjects with edema were available, no definitive conclusions were drawn from this analysis. Also, there were no cases of CHF in the dataset, precluding any analysis of CHF concentration relationship.

1.6 Drug Interactions

Muraglitazar is a substrate for CYP3A4, 2C19, 2C9, 2C8, and 2D6. Clinical drug interaction studies were conducted with a potent inhibitor of CYP3A4 and 2C19 (ketoconazole), and also with an inhibitor of CYP2C8 (gemfibrozil) since these substrates

appear to contribute 73% of the overall oxidative metabolism. No specific studies with inhibitors of 2D6 were conducted because it was considered a minor pathway of muraglitazar metabolism. Co-administration with ketoconazole resulted in a modest increase in the Cmax (12%) and a moderate increase in AUC (43%) of muraglitazar which is unlikely to be of clinical significance. Similarly, co-administration with gemfibrozil resulted in clinically non-significant increases in muraglitazar Cmax (23%) and AUC (26%).

Muraglitazar does not appear to be an inhibitor of CYP2C9 or 2C19. Muraglitazar did not affect the PK of S-warfarin (2C9 substrate), R-warfarin (2C19 substrate) or the pharmacodynamic effects of warfarin. Similarly, muraglitazar did not alter the PK of glyburide (a substrate for 2C9).

Muraglitazar does not appear to affect plasma concentrations of CYP3A4 substrates such as simvastatin or atorvastatin. Following concomitant administration, the PK of muraglitazar or statins (simvastatin, atorvastatin or pravastatin) was not altered by the other agent. Co-administration of muraglitazar with glyburide or metformin did not alter the PK of either agent. Co-administration of muraglitazar with fibrates (fenofibrate or gemfibrozil) did not appear to affect the PK profile either agent. Famotidine did not affect the PK profile of muraglitazar.

In vitro, muraglitazar is not a p-glycoprotein (p-gp) transporter substrate. On the other hand, muraglitazar is a moderate in vitro inhibitor of p-gp with an IC_{50} = 7.1 μM. Since this IC_{50} is approximately 5-fold higher than the mean steady state Cmax concentration produced by a 5 mg muraglitazar dose, drug interaction with p-gp substrates is not anticipated.

1.7 Safety Summary for Clinical Pharmacology Studies

To date, 678 subjects in the Clinical Phamacology program have been exposed to muraglitazar for an average of 8 days. Single oral doses of muraglitazar up to 300 mg in healthy subjects appeared to be safe and well tolerated. Multiple doses of muraglitazar up to 20 mg once daily for 28 days in healthy subjects and subjects with type 2 diabetes appeared to be safe and well tolerated. Although peripheral edema AEs were seen when muraglitazar doses of 20 mg to 50 mg were given for 1 to 4 weeks in the phase 1/2a studies, there were no peripheral edema AEs with 5 mg once daily for 28 days in these studies. There were no episodes of hypoglycemia in either the normoglycemic

nondiabetic or hyperglycemic diabetic subjects who received muraglitazar at doses up to 20 to 50 mg daily for 1 month.

Mild decreases in hematologic parameters were seen with muraglitazar administration at doses ≥ 20 mg. There were no clinically significant differences in serum and urine laboratory parameters between muraglitazar and placebo in healthy or type 2 diabetic subjects in the phase 1/2a studies. Twenty-eight days administration of high doses of muraglitazar (20-50 mg) was associated with mild increases in heart rate (sinus rhythm) in both healthy and diabetic subjects. Doses < 20 mg appeared to be without effect on heart rate, as were single doses of up to 300 mg. Studies with warfarin, ketoconazole, famotidine, glyburide, metformin, gemfibrozil, fenofibrate, pravastatin, simvastatin, and atorvastatin demonstrated no clinically significant effects on the safety profile of muraglitazar when coadministered with these agents. The muraglitazar safety profile appeared to be unaffected by age, gender, race, food or concomitant medication use.

1.8 QTc Study

The effect of muraglitazar on the QTc interval was evaluated in an intensive ECG study in healthy subjects. The main objective was to determine the effect of multiple-dose muraglitazar on the QTcF interval. This double-blind, placebo-controlled study included a positive control (moxifloxacin), and cross-over design with multiple-dose administration of muraglitazar 5 mg or 50 mg for 8 days. Moxifloxacin prolonged QTcF by 16.6 msec more than placebo with a lower 95% confidence interval of 14.1 msec. In contrast, muraglitazar did not result in significant changes in QTcF compared to placebo at either dose (-0.44 msec for 5 mg and 3.9 msec for 50 mg) with upper 95% confidence intervals (2.35 msec for 5 mg and 6.67 msec for 50 mg) that were below the a priori criteria for a positive effect specified in the protocol.

Attachment 8.3.1A: Demographic and Baseline Characteristics of Study Population

5 page(s) excluding cover page

Attachment 8.3.1A: Demographic and Baseline Characteristics of Study Population

Characteristics	Monotherapy (CV168006, 018)			Combination Therapy (CV168021, 022, 025)		
	Any Mur (N= 729)	Non-Mur (N= 366)	Total (N=1095)	Any Mur (N=1409)	Non-Mur (N= 985)	Total (N=2394)
Age						
n	729	366	1095	1409	985	2394
Mean (SD)	53.54 (9.96)	52.54 (9.57)	53.21 (9.84)	55.08 (8.70)	54.61 (9.01)	54.89 (8.83)
Age, n (%)						
<65 years	631 (86.6)	328 (89.6)	959 (87.6)	1182 (83.9)	844 (85.7)	2026 (84.6)
>=65 years	98 (13.4)	38 (10.4)	136 (12.4)	227 (16.1)	141 (14.3)	368 (15.4)
Gender, n (%)						
Male	417 (57.2)	198 (54.1)	615 (56.2)	724 (51.4)	500 (50.8)	1224 (51.1)
Female	312 (42.8)	168 (45.9)	480 (43.8)	685 (48.6)	485 (49.2)	1170 (48.9)
Race, n (%)						
White	595 (81.6)	290 (79.2)	885 (80.8)	1229 (87.2)	878 (89.1)	2107 (88.0)
Black	46 (6.3)	26 (7.1)	72 (6.6)	110 (7.8)	67 (6.8)	177 (7.4)
Other *	88 (12.1)	50 (13.7)	138 (12.6)	70 (5.0)	40 (4.1)	110 (4.6)
Ethnicity, n (%) **						
Hispanic/Latino	142 (19.5)	70 (19.1)	212 (19.4)	432 (30.7)	271 (27.5)	703 (29.4)
Non Hispanic/Latino	430 (59.0)	218 (59.6)	648 (59.2)	977 (69.3)	714 (72.5)	1691 (70.6)
Missing	157 (21.5)	78 (21.3)	235 (21.5)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Appendix 3.1.1 of SCE
Dataset: Randomized Subjects
Note: 'Any Mur' for monotherapy included Mur 1.5 and 5 doses in study CV168006, and Mur 2.5 and 5 mg doses, excluding Open-Label cohort, in study CV168018. 'Any Mur' for combination therapy included Mur 2.5+Gly, Mur 5+Gly, Mur 2.5+Met, and Mur 5+Met in studies CV168021, 022 and 025.
Definition of Metabolic Syndrome based upon NCEP ATP III guidelines.
* Included Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and other.
** For CV168006, ethnicity was collected only for subjects in the Americas (US, Mexico, Canada, Puerto Rico, Brazil, Argentina).
*** Non-fasting values were included for study CV168006.
**** Only fasting measurements are used.

PROGRAM SOURCE: /WWBDM/CLIN/PROJ/CV/168/ISS_ISE/DEV/STATS/DEMOG_01.SAS 26-OCT-2004 09:12

Attachment 8.3.1A: Demographic and Baseline Characteristics of Study Population

Characteristics	Monotherapy (CV168006, 018)			Combination Therapy (CV168021, 022, 025)		
	Any Mur (N= 729)	Non-Mur (N= 366)	Total (N=1095)	Any Mur (N=1409)	Non-Mur (N= 985)	Total (N=2394)
Body Weight (Kg)						
n	729	366	1095	1409	985	2394
Mean (SD)	89.22 (17.95)	89.67 (18.51)	89.37 (18.13)	88.04 (18.31)	89.75 (17.89)	88.75 (18.15)
Body Mass Index						
n	729	366	1095	1409	985	2394
Mean (SD)	31.16 (4.90)	31.55 (4.92)	31.29 (4.91)	31.30 (4.79)	31.67 (4.85)	31.45 (4.82)
Duration of Diabetes, n (%)						
< 5 Years	570 (78.2)	284 (77.6)	854 (78.0)	664 (47.1)	512 (52.0)	1176 (49.1)
>=5 Years	157 (21.5)	80 (21.9)	237 (21.6)	743 (52.7)	473 (48.0)	1216 (50.8)
Missing	2 (0.3)	2 (0.5)	4 (0.4)	2 (0.1)	0 (0.0)	2 (0.1)
Median (Years) (25th, 75th)	1.50 (0.17, 4.00)	1.52 (0.23, 4.22)	1.50 (0.18, 4.00)	5.00 (2.81, 8.00)	4.44 (2.33, 8.00)	5.00 (2.58, 8.00)
HbA1c (%)						
n	727	365	1092	1408	985	2393
Mean (SD)	8.14 (1.05)	8.24 (1.12)	8.17 (1.08)	8.07 (1.02)	8.12 (1.00)	8.09 (1.01)
FPG (mg/dL)						
n	724	364	1088	1408	984	2392
Mean (SD)	178.0 (53.68)	183.8 (51.37)	179.9 (52.96)	172.1 (48.05)	174.1 (49.65)	172.9 (48.71)

Dataset: Randomized Subjects
Note: 'Any Mur' for monotherapy included Mur 1.5 and 5 doses in study CV168006, and Mur 2.5 and 5 mg doses, excluding Open-Label cohort, in study CV168018. 'Any Mur' for combination therapy included Mur 2.5+Gly, Mur 5+Gly, Mur 2.5+Met, and Mur 5+Met in studies CV168021, 022 and 025.
Definition of Metabolic Syndrome based upon NCEP ATP III guidelines.
* Included Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and other.
** For CV168006, ethnicity was collected only for subjects in the Americas (US, Mexico, Canada, Puerto Rico, Brazil, Argentina).
*** Non-fasting values were included for study CV168006.
**** Only fasting measurements are used.

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Attachment 8.3.1A: Demographic and Baseline Characteristics of Study Population

Characteristics	Monotherapy (CV168006, 018)			Combination Therapy (CV168021, 022, 025)		
	Any Mur (N= 729)	Non-Mur (N= 366)	Total (N=1095)	Any Mur (N=1409)	Non-Mur (N= 985)	Total (N=2394)
Fasting Insulin (uU/mL)						
n	681	345	1026	1388	966	2354
Mean (SD)	14.81 (12.09)	14.53 (8.64)	14.72 (11.05)	14.45 (9.62)	15.21 (12.39)	14.76 (10.84)
Fasting C-peptide (ng/mL) ***						
n	681	345	1026	1406	985	2391
Mean (SD)	3.27 (1.45)	3.32 (1.43)	3.29 (1.44)	3.12 (1.24)	3.15 (1.29)	3.13 (1.26)
Systolic BP (mmHg)						
n	729	366	1095	1409	985	2394
Mean (SD)	129.0 (14.75)	129.4 (15.26)	129.1 (14.92)	131.0 (15.04)	131.4 (15.70)	131.2 (15.31)
Diastolic BP (mmHg)						
n	729	366	1095	1409	985	2394
Mean (SD)	79.74 (8.74)	80.09 (8.28)	79.86 (8.59)	80.32 (8.90)	80.41 (8.76)	80.36 (8.84)
Triglycerides (mg/dL) ****						
n	727	365	1092	1409	985	2394
Mean (SD)	188.6 (117.3)	192.7 (129.1)	190.0 (121.3)	202.8 (119.5)	199.2 (137.0)	201.3 (126.9)
Median	158.0	163.5	160.0	174.0	166.0	171.0
(25th, 75th)	(114.0, 232.0)	(109.0, 226.5)	(112.0, 231.0)	(124.0, 244.0)	(119.5, 234.0)	(122.0, 239.5)

Dataset: Randomized Subjects
Note: 'Any Mur' for monotherapy included Mur 1.5 and 5 doses in study CV168006, and Mur 2.5 and 5 mg doses, excluding Open-Label cohort, in study CV168018. 'Any Mur' for combination therapy included Mur 2.5+Gly, Mur 5+Gly, Mur 2.5+Met, and Mur 5+Met in studies CV168021, 022 and 025.
Definition of Metabolic Syndrome based upon NCEP ATP III guidelines.
* Included Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and other.
** For CV168006, ethnicity was collected only for subjects in the Americas (US, Mexico, Canada, Puerto Rico, Brazil, Argentina).
*** Non-fasting values were included for study CV168006.
**** Only fasting measurements are used.

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Attachment 8.3.1A: Demographic and Baseline Characteristics of Study Population

Characteristics	Monotherapy (CV168006, 018)			Combination Therapy (CV168021, 022, 025)		
	Any Mur (N= 729)	Non-Mur (N= 366)	Total (N=1095)	Any Mur (N=1409)	Non-Mur (N= 985)	Total (N=2394)
LDL-C (mg/dL)						
n	727	365	1092	1409	985	2394
Mean (SD)	123.7 (33.37)	128.4 (37.63)	125.3 (34.90)	113.1 (34.36)	112.3 (33.01)	112.8 (33.81)
HDL-C (mg/dL)						
n	727	365	1092	1409	985	2394
Mean (SD)	43.03 (9.90)	43.73 (10.60)	43.26 (10.14)	45.35 (10.50)	45.59 (10.65)	45.45 (10.56)
Non-HDL-C (mg/dL)						
n	727	365	1092	1409	985	2394
Mean (SD)	157.1 (38.91)	162.4 (38.58)	158.9 (38.86)	151.9 (38.85)	150.1 (38.62)	151.1 (38.76)
ApoB (mg/dL)						
n	720	363	1083	1408	985	2393
Mean (SD)	106.3 (33.86)	108.6 (27.49)	107.1 (31.87)	101.8 (24.52)	100.8 (28.39)	101.4 (26.18)
Total-C (mg/dL)						
n	727	365	1092	1409	985	2394
Mean (SD)	200.2 (39.35)	206.1 (39.48)	202.1 (39.48)	197.2 (39.68)	195.7 (38.81)	196.6 (39.33)
FFA (mEq/L)						
n	718	361	1079	1407	984	2391
Mean (SD)	0.58 (0.23)	0.59 (0.22)	0.58 (0.23)	0.67 (0.23)	0.66 (0.25)	0.66 (0.24)

Dataset: Randomized Subjects
Note: 'Any Mur' for monotherapy included Mur 1.5 and 5 doses in study CV168006, and Mur 2.5 and 5 mg doses, excluding Open-Label cohort, in study CV168018. 'Any Mur' for combination therapy included Mur 2.5+Gly, Mur 5+Gly, Mur 2.5+Met, and Mur 5+Met in studies CV168021, 022 and 025.
Definition of Metabolic Syndrome based upon NCEP ATP III guidelines.
* Included Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and other.
** For CV168006, ethnicity was collected only for subjects in the Americas (US, Mexico, Canada, Puerto Rico, Brazil, Argentina).
*** Non-fasting values were included for study CV168006.
**** Only fasting measurements are used.

PROGRAM SOURCE: /wwBDM/CLIN/PROJ/CV/168/ISS_ISE/DEV/STATS/DEMOG_01.SAS 26-OCT-2004 09:12

Attachment 8.3.1A: Demographic and Baseline Characteristics of Study Population

Characteristics	Monotherapy (CV168006, 018)			Combination Therapy (CV168021, 022, 025)		
	Any Mur (N= 729)	Non-Mur (N= 366)	Total (N=1095)	Any Mur (N=1409)	Non-Mur (N= 985)	Total (N=2394)
Use of Statins, n (%)						
No	581 (79.7)	302 (82.5)	883 (80.6)	1066 (75.7)	747 (75.8)	1813 (75.7)
Yes	148 (20.3)	64 (17.5)	212 (19.4)	343 (24.3)	238 (24.2)	581 (24.3)
Use of Fibrates, n (%)						
No	723 (99.2)	365 (99.7)	1088 (99.4)	1397 (99.1)	981 (99.6)	2378 (99.3)
Yes	6 (0.8)	1 (0.3)	7 (0.6)	12 (0.9)	4 (0.4)	16 (0.7)
Use of Diuretics, n (%)						
No	614 (84.2)	306 (83.6)	920 (84.0)	1129 (80.1)	781 (79.3)	1910 (79.8)
Yes	115 (15.8)	60 (16.4)	175 (16.0)	280 (19.9)	204 (20.7)	484 (20.2)
Metabolic Syndrome						
No	245 (33.6)	124 (33.9)	369 (33.7)	465 (33.0)	304 (30.9)	769 (32.1)
Yes	481 (66.0)	240 (65.6)	721 (65.8)	941 (66.8)	669 (67.9)	1610 (67.3)
Unknown	3 (0.4)	2 (0.5)	5 (0.5)	3 (0.2)	12 (1.2)	15 (0.6)

Dataset: Randomized Subjects
Note: 'Any Mur' for monotherapy included Mur 1.5 and 5 doses in study CV168006, and Mur 2.5 and 5 mg doses, excluding Open-Label cohort, in study CV168018. 'Any Mur' for combination therapy included Mur 2.5+Gly, Mur 5+Gly, Mur 2.5+Met, and Mur 5+Met in studies CV168021, 022 and 025.
Definition of Metabolic Syndrome based upon NCEP ATP III guidelines.
* Included Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and other.
** For CV168006, ethnicity was collected only for subjects in the Americas (US, Mexico, Canada, Puerto Rico, Brazil, Argentina).
*** Non-fasting values were included for study CV168006.
**** Only fasting measurements are used.

PROGRAM SOURCE: /wwBDM/CLIN/PROJ/CV/168/ISS_ISE/DEV/STATS/DEMOG_01.SAS 26-OCT-2004 09:12

Attachment 8.4.4: Listing of Deaths in Muraglitazar Phase 2 and 3 Studies (Complete Dataset)

2 page(s) excluding cover page

Attachment 8.4.4: Listing of Deaths in Muraglitazar Phase 2 and 3 Studies (Complete Dataset)

Subject ID	Age/ Gender	Dose at Onset	Duration of Exposure (Days)	Day at Which Death Occurred (Days)	Cause of Death / Associated Diagnoses
Subjects with type 2 diabetes					
CV168006-5-3	62/F	Muraglitazar 10 mg	112	112	Motor vehicle accident / NA
CV168006-10-1	66/M	Pioglitazone 15 mg	715	716	Throat cancer / tobacco use for 45 years, prior history of alcohol abuse
CV168006-11-8	59/M	Muraglitazar 20 mg	49	60	Myocardial infarction / hypertension
CV168006-80-9	70/F	Muraglitazar 5 mg	806	808	Lung cancer metastatic / COPD, tobacco use, recurrent bronchitis
CV168006-255-1	69/M	Muraglitazar 1.5 mg	473	505	Pulmonary carcinoma / wasting syndrome, previous surgical removal of anaplastic stomach cancer
CV168006-267-5	69/F	Muraglitazar 1.5 mg	549	578	Acute myeloid leukemia / NA
CV168021-33-5	62/M	Placebo plus glyburide 15 mg	244	244	Pulmonary embolus / venous thrombosis
CV168021-237-5	56/F	Muraglitazar 5 mg plus glyburide 10 mg	307	321	Cardiac failure acute, acute myocardial infarction, bradycardia, ventricular fibrillation
CV168021-298-21	44/M	Muraglitazar 5 mg plus glyburide 15 mg	29	29	Gun shot wound/ NA
CV168022-142-4	63/F	Muraglitazar 5mg plus metformin 2000 mg	206	326	Small cell lung cancer metastatic to brain, adrenal, and liver
CV168022-153-2	54/M	Muraglitazar 5 mg plus metformin 2000 mg	115	125	Myocardial infarction / hypertension, coronary artery disease

Attachment 8.4.4: Listing of Deaths in Muraglitazar Phase 2 and 3 Studies (Complete Dataset)

Subject ID	Age/ Gender	Dose at Onset	Duration of Exposure (Days)	Day at Which Death Occurred (Days)	Cause of Death / Associated Diagnoses
CV168022-250-15	49/M	Muraglitazar 2.5 mg plus metformin 1500 mg	197	224	Hepatic neoplasm malignant
CV168022-256-6	56/F	Muraglitazar 5 mg plus metformin 1500 mg	45	149	Metastatic breast cancer, cardiopulmonary arrest
CV168022-287-1	52/M	Muraglitazar 2.5 mg plus metformin 2000 mg	10	10	Myocardial infarction / NA
CV168025-193-9	66/F	Muraglitazar 5 mg plus metformin 2000 mg	201	202	Myocardial infarction, sudden cardiac death / cardiac failure
CV168025-193-10	61/M	Muraglitazar 5 mg plus metformin 2000 mg	205	208	Not specified[a] / history of myocardial infarction, peripheral vascular disease
CV168025-241-3	67/M	Muraglitazar 5 mg plus metformin 1500 mg	143	144	Sudden death / chronic ischemic heart disease
CV168025-241-38	60/F	Muraglitazar 5 mg plus metformin 2000 mg	291	293	Hemorrhagic stroke / hypertension, ischemic heart disease
CV168025-242-29	67/M	Pioglitazone 30 mg plus metformin 2500 mg	36	39	Perforated ulcer / urinary calculus
CV168025-288-65	50/F	Muraglitazar 5 mg plus metformin 2500 mg	112	220	Head of pancreas carcinoma with metastasis / cholestasis
CV168025-314-1	53/M	Muraglitazar 5 mg plus metformin 1500 mg	107	110	Stroke and hemiplegia / hypertension

a. Site stated “subject found dead.” Cause of death was not specified and no further information is available.

Attachment 8.4.5: Listing of All Reported Malignant Neoplasms, All Subjects in Phase 2 and 3 Studies

6 page(s) excluding cover page

Attachment 8.4.5: Listing of All Reported Malignant Neoplasms, All Subjects in Phase 2 and 3 Studies

PREFERRED TERM	PROTOCOL-SITE-PAT	AGE/ GENDER	TREATMENT GROUP AT REPORT	DAYS SINCE FIRST DOSE	OUTCOME	LOCATION OF NARRATIVE DESCRIPTION
ACUTE LYMPHOCYTIC LEUKAEMIA	CV168018-140-1	57/F	PLACEBO	33	DID NOT RESOLVE	
ACUTE MYELOID LEUKAEMIA	CV168006-267-5	69/F	BMS1.50	537	DEATH	
ADRENAL NEOPLASM	CV168025-235-14	67/F	PI30/ME1500	230		
BASAL CELL CARCINOMA	CV168006-108-3	64/F	BMS5	748	RESOLVED	
	CV168006-110-1	66/F	BMS5	219		
	CV168006-336-1	63/M	PIO15	489	RESOLVE	
	CV168018-52-1	67/F	MU5 OL	33	RESOLVED	
	CV168021-305-2	69/M	MU2.5/GL15	236	RESOLVED	
	CV168025-231-13	57/M	MU5/ME2500	36	RESOLVED	
BLADDER CANCER	CV168006-226-9	66/M	BMS10	573	DID NOT RESOLVE	
	CV168006-336-6	71/M	BMS10	58	DID NOT RESOLVE	
	CV168025-123-4	62/M	PI30/ME1500	170	DID NOT RESOLVE	
BLADDER CANCER RECURRENT	CV168006-265-4	63/M	PIO45	256	RESOLVED	

Data set: Treated Subjects and Open-Label Cohort
Includes all reported malignant neoplasms up to 30 days post ST Phase, or post ST combined with LT Phase for subjects who started LT.
Includes CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT.
Duplicate events are printed.

PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_neoplas.sas MEDDRA VERSION: 8 19JUL05 08:53

Attachment 8.4.5: Listing of All Reported Malignant Neoplasms, All Subjects in Phase 2 and 3 Studies

PREFERRED TERM	PROTOCOL-SITE-PAT	AGE/ GENDER	TREATMENT GROUP AT REPORT	DAYS SINCE FIRST DOSE	OUTCOME	LOCATION OF NARRATIVE DESCRIPTION
BRAIN NEOPLASM	CV168021-217-13	54/F	PST MU5/PST GL15	43	DID NOT RESOLVE	
BREAST CANCER	CV168006-100-1	54/F	BMS1.50	86	RESOLVED	
	CV168021-119-13	66/F	MU2.5/GL15	74	UNKNOWN	
	CV168025-81-5	64/F	MU5/ME1500	203		
BREAST CANCER METASTATIC	CV168022-256-6	56/F	MU5/ME1500	27	DEATH	
CERVIX CARCINOMA	CV168025-351-3	56/F	MU5/ME1500	307	DID NOT RESOLVE	
ENDOMETRIAL CANCER	CV168006-100-1	54/F	BMS1.50	92	RESOLVED	
	CV168006-267-17	65/F	BMS10	23	RESOLVED, WITH SEQUELA	
HEPATIC NEOPLASM MALIGNANT	CV168022-250-15	49/M	MU2.5/ME1500	191	DEATH	
LUNG CANCER METASTATIC	CV168006-80-9	70/F	BMS5	752	DEATH	

Data set: Treated Subjects and Open-Label Cohort
Includes all reported malignant neoplasms up to 30 days post ST Phase, or post ST combined with LT Phase for subjects who started LT.
Includes CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT.
Duplicate events are printed.

PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_neoplas.sas MEDDRA VERSION: 8 19JUL05 08:53

Attachment 8.4.5: Listing of All Reported Malignant Neoplasms, All Subjects in Phase 2 and 3 Studies

PREFERRED TERM	PROTOCOL-SITE-PAT	AGE/ GENDER	TREATMENT GROUP AT REPORT	DAYS SINCE FIRST DOSE	OUTCOME	LOCATION OF NARRATIVE DESCRIPTION
LUNG NEOPLASM MALIGNANT	CV168006-255-1	69/M	PST BMS1.50	476	DEATH	
	CV168021-96-10	54/F	MU5/GL15	75	DID NOT RESOLVE	
MALIGNANT MELANOMA	CV168018-32-4	70/M	MU5	46	RESOLVED	
	CV168021-256-1	62/F	MU5/GL15	344	RESOLVED	
NEOPLASM PROSTATE	CV168006-336-6	71/M	BMS10	8		
NEOPLASM SKIN	CV168006-413-1	46/F	BMS10	827		
OESOPHAGEAL CARCINOMA	CV168006-239-5	57/M	BMS10	436	DID NOT RESOLVE	
	CV168006-322-18	58/F	BMS5	447	DID NOT RESOLVE	
OVARIAN CANCER	CV168025-241-17	64/F	PST MU5/PST ME2500	307	DID NOT RESOLVE	

Data set: Treated Subjects and Open-Label Cohort
Includes all reported malignant neoplasms up to 30 days post ST Phase, or post ST combined with LT Phase for subjects who started LT.
Includes CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT.
Duplicate events are printed.

PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_neoplas.sas MEDDRA VERSION: 8 19JUL05 08:53

Attachment 8.4.5: Listing of All Reported Malignant Neoplasms, All Subjects in Phase 2 and 3 Studies

PREFERRED TERM	PROTOCOL-SITE-PAT	AGE/ GENDER	TREATMENT GROUP AT REPORT	DAYS SINCE FIRST DOSE	OUTCOME	LOCATION OF NARRATIVE DESCRIPTION
PANCREATIC CARCINOMA	CV168025-288-65	50/F	PST MU5/PST ME2500	114	DEATH	
PANCREATIC CARCINOMA METASTATIC	CV168025-241-2	60/M	MU5/ME2500	84	DID NOT RESOLVE	
PANCREATIC NEOPLASM	CV168006-325-3	49/M	PST BMS1.50	52	RESOLVED, WITH SEQUELA	
	CV168006-325-3	49/M	PST BMS1.50	55	DID NOT RESOLVE	
PROSTATE CANCER	CV168006-23-10	55/M	BMS1.50	933	DID NOT RESOLVE	
	CV168006-115-3	66/M	BMS20	27	RESOLVED	
	CV168006-272-1	66/M	PIO15	610	DID NOT RESOLVE	
	CV168006-336-6	71/M	BMS10	254	DID NOT RESOLVE	
	CV168018-100-3	70/M	MU2.5	132	DID NOT RESOLVE	
	CV168025-31-17	53/M	PI30/ME1500	236	DID NOT RESOLVE	

Data set: Treated Subjects and Open-Label Cohort
Includes all reported malignant neoplasms up to 30 days post ST Phase, or post ST combined with LT Phase for subjects who started LT.
Includes CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT.
Duplicate events are printed.

PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_neoplas.sas MEDDRA VERSION: 8 19JUL05 08:53

Attachment 8.4.5: Listing of All Reported Malignant Neoplasms, All Subjects in Phase 2 and 3 Studies

PREFERRED TERM	PROTOCOL-SITE-PAT	AGE/ GENDER	TREATMENT GROUP AT REPORT	DAYS SINCE FIRST DOSE	OUTCOME	LOCATION OF NARRATIVE DESCRIPTION
PROSTATE CANCER	CV168025-231-8	60/M	PI30/ME2000	318	DID NOT RESOLVE	
	CV168025-231-10	56/M	MU5/ME2500	283	DID NOT RESOLVE	
	CV168025-288-62	66/M	PST PI30/PST ME2000	37	RESOLVED	
SMALL CELL LUNG CANCER METASTATIC	CV168021-258-1	65/M	MU2.5/GL15	342	DID NOT RESOLVE	
	CV168022-142-4	63/F	MU5/ME2000	206	DEATH	
SQUAMOUS CELL CARCINOMA	CV168022-139-2	59/F	MU5/ME2000	502	RESOLVED, WITH SEQUELA	
THROAT CANCER	CV168006-10-1	66/M	PIO15	679	DEATH	
THYROID NEOPLASM*	CV168006-114-1	58/M	BMS20	140		
	CV168018-31-5	51/M	PST MU5	154		

Data set: Treated Subjects and Open-Label Cohort
Includes all reported malignant neoplasms up to 30 days post ST Phase, or post ST combined with LT Phase for subjects who started LT.
Includes CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT.
Duplicate events are printed.
* These cases were considered benign by the investigator

PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_neoplas.sas MEDDRA VERSION: 8 19JUL05 08:53

Attachment 8.4.5: Listing of All Reported Malignant Neoplasms, All Subjects in Phase 2 and 3 Studies

PREFERRED TERM	PROTOCOL-SITE-PAT	AGE/ GENDER	TREATMENT GROUP AT REPORT	DAYS SINCE FIRST DOSE	OUTCOME	LOCATION OF NARRATIVE DESCRIPTION
THYROID NEOPLASM*	CV168021-119-13	66/F	MU2.5/GL15	242		
	CV168021-156-1	66/F	MU5/GL15	103		
	CV168022-67-2	68/F	PST PLA/PST ME1500	111		
	CV168022-78-3	68/F	MU2.5/ME1500	169		

Data set: Treated Subjects and Open-Label Cohort
Includes all reported malignant neoplasms up to 30 days post ST Phase, or post ST combined with LT Phase for subjects who started LT.
Includes CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT.
Duplicate events are printed.
* These cases were considered benign by the investigator

PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_neoplas.sas MEDDRA VERSION: 8 19JUL05 08:53

Attachment 8.4.6A: Listing of Preferred Term Codes in Cardiovascular Events Special Search Category

2 page(s) excluding cover page

PROTOCOL: CV168 FDA AD COM PAGE: 1

ATTACHMENT 8.4.6A: LISTING OF PREFERRED TERM CODES IN CARDIOVASCULAR EVENTS SPECIAL SEARCH CATEGORY

Obs	PT_CODE	CONCEPT	LEVEL	MURAGLIT
1	10000891	acute myocardial infarction	PT	MI
2	10001903	amaurosis fugax	PT	TIA
3	10002383	angina pectoris	PT	CAD
4	10002388	angina unstable	PT	CAD
5	10006147	brain stem infarction	PT	Stroke
6	10008034	cerebellar infarction	PT	Stroke
7	10008118	cerebral infarction	PT	Stroke
8	10008190	cerebrovascular accident	PT	Stroke
9	10011076	coronary artery atherosclerosis		CAD
10	10011078	coronary artery disease	PT	CAD
11	10011086	coronary artery occlusion	PT	CAD
12	10011089	coronary artery stenosis	PT	CAD
13	10011090	coronary artery surgery	PT	Coronary Revascularization
14	10011091	cornoary artery thrombosis	PT	CAD
15	10011101	coronary endartectomy	PT	Coronary Revascularization
16	10011105	coronary ostial stenosis	PT	CAD
17	10014498	embolic stroke	PT	Stroke
18	10019005	haemorrhagic cerebral infarction	PT	Stroke
19	10019016	haemorrhagic stroke	PT	Stroke
20	10028596	myocardial infarction	PT	MI
21	10028600	mtocardial ischaemia	PT	CAD
22	10033697	papillary muscle infarction	PT	MI
23	10035092	pituitary infarction	PT	Stroke
24	10037721	quadruple vessel bypass graft	PT	Coronary Revascularization
25	10040730	single vessel bypass graft	PT	Coronary Revascularization
26	10043647	thrombotic stroke	PT	Stroke
27	10044390	transient ischaemic attack	PT	TIA

DATA SET: Cardiovasculr SSC at FDA AD COM full integration
MEDDRA VERSION: 8.0

PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvssc.sas 03JUN05 09:50

PROTOCOL: CV168 FDA AD COM PAGE: 2

ATTACHMENT 8.4.6A: LISTING OF PREFERRED TERM CODES IN CARDIOVASCULAR EVENTS SPECIAL SEARCH CATEGORY

Obs	PT_CODE	CONCEPT	LEVEL	MURAGLIT
28	10044675	triple vessel bypass graft	PT	Coronary Revascularization
29	10049418	sudden cardiac death	PT	Coronory Death
30	10049768	silent myocardial infarction	PT	MI
31	10049887	coronary revascularization	PT	Coronary Revascularization
32	10049993	cardiac death	PT	Coronory Death
33	10050329	coronary angiolasty	PT	Coronary Revascularization
34	10050496	reversible ischaemic neurologic deficit	PT	TIA
35	10051078	lacunar infarction	PT	Stroke
36	10051198	double vessel bypass graft	PT	Coronary Revascularization
37	10051592	acute coronary syndrome	PT	CAD
38	10052086	coronary aterial stent insertion	PT	Coronary Revascularization
39	10052895	coronary artery insufficiency	PT	CAD
40	10053261	coronary artery reocclusion	PT	CAD
41	10055677	haemorrhagic transformation stroke	PT	Stroke
42	10055803	haemorrhage coronary artery	PT	CAD
43	10057613	thromboembolic stroke	PT	Stroke
44	10058144	postinfarction angina	PT	CAD
45	10058145	subendocardail ischaemia	PT	CAD
46	10059025	coronary bypass thrombosis	PT	CAD
47	10059211	transmyocardial revascularization	PT	Coronary Revascularization
48	10059613	stroke in evolution	PT	Stroke
49	10060839	embolic cerebral infarction	PT	Stroke
50	10060840	ischaemic cerebral infarction	PT	Stroke
51	10061256	ischaemic stroke	PT	Stroke

DATA SET: Cardiovasculr SSC at FDA AD COM full integration
MEDDRA VERSION: 8.0

PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvssc.sas 03JUN05 09:50

Attachment 8.4.6.1A: Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term PhaseProtocol CV168006

21 page(s) excluding cover page

PROTOCOL: CV168 FDA AD COM PAGE: 1

Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168006

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168006-3-3	62/M	4.282	ANGINA UNSTABLE	BMS1.50	LT	458	3	SAE	NO
CV168006-11-8	59/M	1.436	MYOCARDIAL INFARCTION	BMS20	ST	49	4	SAE	YES
			CARDIOVASCULAR DEATH	PST BMS20	PST ST	60			
CV168006-24-4	50/F	2.801	MYOCARDIAL INFARCTION	BMS10	LT	825	3	SAE	NO
CV168006-32-3	57/M	12.060	CORONARY ARTERY STENOSIS	BMS1.50	LT	694	3	AE	NO
			CORONARY ARTERY STENOSIS	BMS1.50	LT	694	3	SAE	NO
CV168006-35-2	48/M	0.979	ANGINA PECTORIS	BMS1.50	ST	14	2	AE	NO
CV168006-39-3	63/M	1.025	CORONARY ARTERY DISEASE	BMS10	LT	593	3	SAE	NO
CV168006-40-2	55/F	18.560	TRANSIENT ISCHAEMIC ATTACK	BMS1.50	LT	741	2	AE	NO
CV168006-46-5	52/F	21.290	ANGINA UNSTABLE	BMS5	LT	905	3	SAE	NO
CV168006-48-4	52/M	14.770	ANGINA PECTORIS	BMS5	LT	740	3	SAE	NO

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
Includes events that occurred during the Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

PROTOCOL: CV168 FDA AD COM PAGE: 2

Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168006

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168006-48-4	52/M		CORONARY ARTERY DISEASE	BMS5	LT	740	3	SAE	NO
			CORONARY ARTERY STENOSIS	BMS5	LT	740	3	SAE	NO
CV168006-51-2	60/M	2.128	CORONARY ARTERY DISEASE	BMS20	LT	558	3	SAE	NO
CV168006-67-3	63/M	1.670	MYOCARDIAL ISCHAEMIA	BMS10	LT	918	3	AE	NO
			CORONARY ARTERY DISEASE	BMS10	LT	924	4	SAE	NO
CV168006-106-1	64/F	3.238	ANGINA PECTORIS	BMS1.50	LT	326	1	AE	NO
			CORONARY ARTERY DISEASE	BMS1.50	LT	368	1	AE	NO
			ANGINA PECTORIS	BMS1.50	LT	935	1	AE	NO
CV168006-114-5	54/F	1.905	ANGINA PECTORIS	BMS10	ST	62	1	AE	NO
CV168006-115-3	66/M	1.223	MYOCARDIAL INFARCTION	BMS20	LT	244	3	SAE	NO
			CORONARY ARTERY DISEASE	BMS20	LT	251	3	AE	NO

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
Includes events that occurred during the Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

PROTOCOL: CV168 FDA AD COM PAGE: 3

Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168006

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168006-123-3	61/M	9.259	CORONARY ARTERY OCCLUSION	PST BMS5	PST LT	1022	2	SAE	NO
CV168006-130-4	65/F	0.319	CORONARY ARTERY DISEASE	BMS20	LT	213	2	SAE	YES
CV168006-132-1	56/F	0.163	ANGINA PECTORIS	BMS5	LT	817	3	SAE	NO
CV168006-134-1	64/M	0.294	TRANSIENT ISCHAEMIC ATTACK	BMS5	ST	88	1	AE	NO
CV168006-147-6	59/M	2.019	MYOCARDIAL ISCHAEMIA	BMS1.50	LT	461	3	SAE	NO
CV168006-164-3	55/M	2.970	MYOCARDIAL INFARCTION	BMS10	LT	610	3	SAE	NO
CV168006-164-6	62/M	2.047	MYOCARDIAL INFARCTION	BMS20	ST	92	3	SAE	NO
			CORONARY ARTERY DISEASE	BMS20	ST	148	3	SAE	NO
CV168006-188-2	54/M	0.569	CORONARY ARTERY DISEASE	PIO15	ST	139	2	AE	NO
			MYOCARDIAL INFARCTION	PIO15	ST	139	3	SAE	NO

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
Includes events that occurred during the Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168006

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168006-188-4	64/M	2.047	MYOCARDIAL ISCHAEMIA	BMS1.50	LT	169	1	AE	NO
			MYOCARDIAL ISCHAEMIA	BMS1.50	LT	195	2	AE	NO
			CORONARY ARTERY DISEASE	BMS5	LT	289	3	SAE	NO
			CEREBROVASCULAR ACCIDENT	BMS5	LT	363	2	SAE	NO
CV168006-195-8	59/F		CORONARY ARTERY DISEASE	BMS1.50	LT	409	2	AE	NO
CV168006-196-21	54/F		ANGINA UNSTABLE	BMS20	ST	121	3	SAE	YES
CV168006-197-2	48/M		ANGINA PECTORIS	BMS10	ST	23	2	AE	NO
			ANGINA PECTORIS	BMS10	ST	49	2	AE	NO
			ANGINA PECTORIS	BMS10	ST	53	2	AE	NO
			CORONARY ARTERY OCCLUSION	BMS10	ST	57	2	AE	NO
			CORONARY ARTERY OCCLUSION	BMS10	ST	57	2	AE	NO
			ANGINA PECTORIS	BMS10	ST	61	1	AE	NO
			ANGINA PECTORIS	BMS10	ST	62	2	AE	NO
			ANGINA PECTORIS	BMS10	ST	63	2	AE	NO
			CORONARY ARTERY OCCLUSION	BMS10	ST	64	2	SAE	NO
			ANGINA PECTORIS	BMS20	RESCU S	126	2	AE	NO

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
Includes events that occurred during the Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168006

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168006-197-2	48/M		ANGINA PECTORIS	BMS20	RESCU S	127	2	AE	NO
			ANGINA PECTORIS	BMS20	RESCU S	128	2	AE	NO
			ANGINA PECTORIS	BMS20	RESCU S	132	2	AE	NO
			ANGINA PECTORIS	BMS20	RESCU S	140	2	AE	NO
			ANGINA PECTORIS	BMS20	RESCU S	141	1	AE	NO
			ANGINA PECTORIS	BMS20	RESCU S	142	1	AE	NO
			ANGINA PECTORIS	BMS20	RESCU S	147	2	AE	NO
			ANGINA PECTORIS	BMS20	RESCU S	148	2	AE	NO
			ANGINA PECTORIS	BMS20	RESCU S	151	2	AE	NO
			ANGINA PECTORIS	BMS20	LT	208	2	AE	NO
			ANGINA PECTORIS	BMS20	LT	209	2	AE	NO
			ANGINA PECTORIS	BMS20	LT	210	2	AE	NO
			ANGINA PECTORIS	BMS20	LT	220	2	AE	NO
			ANGINA PECTORIS	BMS20	LT	222	2	AE	NO
			ANGINA PECTORIS	BMS20	LT	223	2	AE	NO
			ANGINA PECTORIS	BMS20	LT	224	2	AE	NO
			ANGINA PECTORIS	BMS20	LT	231	2	AE	NO
			ANGINA PECTORIS	BMS20	LT	233	2	AE	NO
			ANGINA PECTORIS	BMS20	LT	234	2	AE	NO
			CORONARY ARTERY OCCLUSION	BMS20	LT	249	2	AE	NO
			CORONARY ARTERY OCCLUSION	BMS20	LT	281	2	SAE	NO
CV168006-198-4	68/F		ANGINA PECTORIS	PIO15	LT	889	2	AE	NO

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
Includes events that occurred during the Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168006

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168006-203-21	61/M		ANGINA PECTORIS	BMS10	ST	136	1	AE	NO
CV168006-205-11	48/M		ANGINA UNSTABLE	BMS20	LT	204	2	SAE	NO
CV168006-234-10	46/F		ANGINA PECTORIS	BMS10	LT	468	2	AE	NO
CV168006-256-2	47/M		CEREBROVASCULAR ACCIDENT	BMS20	ST	28	4	SAE	NO
CV168006-260-3	66/M		ANGINA PECTORIS	BMS10	LT	828	1	SAE	NO
CV168006-267-7	59/F		AMAUROSIS FUGAX	BMS1.50	LT	246	2	AE	NO
CV168006-267-10	58/M		ANGINA PECTORIS	PIO15	ST	137	2	AE	NO
			ANGINA UNSTABLE	PIO15	LT	170	3	SAE	NO
CV168006-304-5	63/M		CEREBROVASCULAR ACCIDENT	PIO15	LT	449	2	SAE	NO
CV168006-320-11	50/F		CEREBROVASCULAR ACCIDENT	BMS10	LT	377	3	SAE	NO
CV168006-322-1	42/M		ANGINA PECTORIS	BMS5	LT	650	1	SAE	NO

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
Includes events that occurred during the Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168006

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168006-322-8	49/M		CORONARY ARTERY DISEASE	BMS10	LT	257	3	SAE	NO
CV168006-325-2	69/M		MYOCARDIAL ISCHAEMIA	PIO15	LT	223	1	AE	NO
CV168006-339-1	55/M	5.829	MYOCARDIAL ISCHAEMIA	BMS5	ST	87	2	AE	NO
			ANGINA UNSTABLE	BMS5	ST	91	2	SAE	NO
CV168006-398-2	60/M	1.462	ANGINA PECTORIS	BMS10	LT	351	2	AE	NO
CV168006-407-3	65/F		ANGINA PECTORIS	BMS1.50	ST	32	1	AE	NO

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
Includes events that occurred during the Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Double-Blind Phase and in the Open-Label Cohort
Protocol CV168018

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168018-50-9	50/F	1.271	ACUTE MYOCARDIAL INFARCTION	PLACEBO	DB	161	3	SAE	NO
CV168018-54-4	63/M	1.502	ANGINA PECTORIS	PST MU5	PST DB	174	1	SAE	NO
CV168018-68-7	57/M	0.360	CORONARY ARTERY DISEASE	MU2.5	DB	131	2	SAE	NO
CV168018-82-10	66/M	0.469	HAEMORRHAGIC STROKE	MU2.5	DB	132	1	SAE	NO
			TRANSIENT ISCHAEMIC ATTACK	MU2.5	DB	132	1	AE	NO
CV168018-112-10	46/M	14.520	CORONARY ARTERY OCCLUSION	MU5	DB	164	3	SAE	NO
CV168018-142-12	54/M	7.836	ANGINA PECTORIS	MU5 OL	OL	5	2	SAE	YES

Data set: Treated Subjects and Open-Label Cohort
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
Includes events that occurred during the Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168021

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168021-11-13	46/M	0.908	MYOCARDIAL ISCHAEMIA	MU5/GL15	ST	85	3	SAE	YES
CV168021-23-3	61/M	2.012	ACUTE MYOCARDIAL INFARCTION	PLA/GL15	LT	169	3	SAE	YES
CV168021-33-5	62/M	0.709	CARDIOVASCULAR DEATH	PST PLA/PST GL15	PST LT	244			
CV168021-34-1	61/M	1.479	CORONARY ARTERY DISEASE	PLA/GL15	LT	199	2	AE	NO
			CORONARY ARTERY DISEASE	PLA/GL15	LT	199	2	AE	NO
			CORONARY ARTERY OCCLUSION	PLA/GL15	LT	199	3	AE	NO
CV168021-34-3	55/M	1.507	ACUTE MYOCARDIAL INFARCTION	MU5/GL5	LT	313	3	SAE	YES
CV168021-40-3	55/M	0.576	CORONARY ARTERY STENOSIS	MU5/GL15	LT	447	3	SAE	NO
CV168021-55-2	65/M	0.475	MYOCARDIAL INFARCTION	MU2.5/GL15	LT	410	3	SAE	YES

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
Includes events that occurred during the Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.

Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168021

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168021-63-3	62/M	1.796	CORONARY ARTERY DISEASE	PST MU5/PST GL15	PST ST	111	3	SAE	NO
			CORONARY ARTERY DISEASE	PST MU5/PST GL15	PST ST	112	1	AE	YES
CV168021-87-5	70/M	5.338	ANGINA PECTORIS	MU5/GL15	ST	17	2	SAE	NO
			ANGINA PECTORIS	MU5/GL15	ST	37	1	AE	NO
			ANGINA PECTORIS	MU5/GL10	ST	56	1	AE	NO
			ANGINA PECTORIS	PST MU5/PST GL10	PST ST	66	3	SAE	NO
CV168021-117-2	67/M	0.697	CORONARY ARTERY DISEASE	MU2.5/GL15	LT	193	2	SAE	NO
CV168021-119-10	61/M	1.152	CORONARY ARTERY DISEASE	PST PLA/PST GL15	PST ST	65	1	AE	NO
CV168021-119-15	64/M	2.243	MYOCARDIAL INFARCTION	PST MU2.5/GL15	PST ST	85	3	SAE	NO
CV168021-132-5	60/M	2.092	CEREBROVASCULAR ACCIDENT	MU5/GL15	ST	139	2	SAE	NO
			ANGINA PECTORIS	MU5/GL5	LT	313	3	SAE	NO
			ANGINA PECTORIS	MU5/GL5	LT	350	2	AE	NO

Data set: Treated Subjects
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Includes events that occurred during the Lead-In Phase.
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Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168021

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168021-141-14	59/F	0.868	CEREBROVASCULAR ACCIDENT	PST MU2.5/PST GL15	PST ST	9	1	SAE	YES
CV168021-145-10	69/M	3.095	CORONARY ARTERY DISEASE	MU2.5/GL15	LT	186	2	AE	NO
CV168021-190-3	52/F	5.220	TRANSIENT ISCHAEMIC ATTACK	MU2.5/GL10	ST	31	3	SAE	NO
CV168021-192-3	52/F	1.940	TRANSIENT ISCHAEMIC ATTACK	MU5/GL15	ST	78	1	AE	NO
CV168021-209-10	47/F	1.550	ANGINA PECTORIS	MU2.5/GL10	LT	358	2	AE	YES
			ACUTE MYOCARDIAL INFARCTION	PST MU2.5/PST GL10	PST LT	398	3	SAE	NO
CV168021-217-13	54/F	13.580	CEREBROVASCULAR ACCIDENT	MU5/PST GL15	ST	26	3	SAE	YES
CV168021-237-5	56/F	0.450	ACUTE MYOCARDIAL INFARCTION	MU5/GL10	LT	307	4	SAE	NO
			CARDIOVASCULAR DEATH	PST MU5/PST GL10	PST LT	321			

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Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168021

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168021-241-7	65/M	3.616	CORONARY ARTERY OCCLUSION	MU2.5/GL15	LT	314	3	AE	NO
CV168021-243-7	68/M	31.080	MYOCARDIAL INFARCTION	MU5/GL15	ST	1	2	SAE	YES
CV168021-244-1	64/M	1.720	ANGINA UNSTABLE	MU2.5/GL15	ST	11	3	SAE	NO
CV168021-244-14	55/M	1.200	ANGINA PECTORIS	MU5/GL15	LT	459	3	SAE	NO
CV168021-281-4	65/M	4.360	CEREBROVASCULAR ACCIDENT	MU2.5/GL15	LT	177	2	SAE	YES
CV168021-282-4	61/M	0.290	MYOCARDIAL INFARCTION	MU5/GL5	LT	402	3	SAE	YES
CV168021-301-34	65/M	0.950	CORONARY ARTERY OCCLUSION	MU5/GL5	LT	403	3	SAE	NO
CV168021-301-38	47/M	2.050	ANGINA PECTORIS	PST MU2.5/PST GL15	PST LT	284	3	SAE	NO
			ANGINA PECTORIS	PST MU2.5/PST GL15	P-LT>30	291	3	SAE	NO
			CORONARY ARTERY OCCLUSION	PST MU2.5/PST GL15	P-LT>30	292	2	SAE	NO

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
Includes events that occurred during the Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168021

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168021-303-40	60/F	7.060	ANGINA PECTORIS	PLA LI/GL15 LI	LEAD-IN	-7	2	AE	NO
CV168021-330-15	67/M	3.663	ACUTE CORONARY SYNDROME	PLA/GL15	LT	291	2	SAE	NO

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
Includes events that occurred during the Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168022

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168022-13-4	62/F	2.648	CORONARY ARTERY DISEASE	PLA/ME2000	LT	475	3	SAE	NO
			CORONARY ARTERY DISEASE	PLA/ME2000	LT	476	2	AE	NO
CV168022-21-4	63/M	3.061	ACUTE MYOCARDIAL INFARCTION	MU5/ME1500	LT	359	4	SAE	NO
CV168022-27-1	64/M	11.912	MYOCARDIAL INFARCTION	MU5/ME2000	LT	229	4	SAE	YES
			MYOCARDIAL INFARCTION	MU5/ME2000	LT	229	4	SAE	YES
CV168022-44-2	70/M	0.348	CORONARY ARTERY OCCLUSION	PLA/ME2000	LT	455	3	SAE	NO
CV168022-49-7	67/M	0.296	MYOCARDIAL INFARCTION	MU2.5/ME2000	ST	135	2	SAE	YES
CV168022-52-10	55/M	0.930	CORONARY ARTERY OCCLUSION	MU2.5/ME2500	ST	125	1	AE	NO
			CORONARY ARTERY OCCLUSION	MU2.5/ME2500	LT	179	1	SAE	NO

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
Includes events that occurred during the Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168022

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168022-69-6	50/M	2.226	TRANSIENT ISCHAEMIC ATTACK	PLA/ME2000	LT	390	3	SAE	NO
CV168022-73-4	66/M	0.443	CORONARY ARTERY STENOSIS	MU5/ME1500	LT	316	2	SAE	NO
			ANGINA PECTORIS	MU5/ME1500	LT	350	2	SAE	NO
			CORONARY ARTERY DISEASE	MU5/ME1500	LT	350	2	SAE	NO
CV168022-83-3	48/M	2.338	ANGINA PECTORIS	PLA/ME2000	ST	60	1	AE	NO
			CORONARY ARTERY OCCLUSION	PLA/ME2000	ST	116	3	SAE	NO
CV168022-124-7	54/F	3.159	ANGINA PECTORIS	PLA/ME1500	ST	134	1	AE	NO
CV168022-128-8	53/F	0.560	CORONARY ARTERY OCCLUSION	MU2.5/ME2500	LT	476	3	SAE	NO
CV168022-153-2	54/M	2.364	MYOCARDIAL INFARCTION	PST MU5/PST ME2000	PST ST	125	4	SAE	NO
			CARDIOVASCULAR DEATH	PST MU5/PST ME2000	PST ST	125			
CV168022-179-3	53/M	1.340	MYOCARDIAL ISCHAEMIA	PST MU5/PST ME2000	PST ST	13	2	SAE	YES

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
Includes events that occurred during the Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168022

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168022-180-7	55/M	1.300	CORONARY ARTERY DISEASE	MU5/ME2000	LT	169	2	SAE	NO
			CORONARY ARTERY DISEASE	MU5/ME2000	LT	206	2	SAE	NO
CV168022-195-1	53/M	4.871	MYOCARDIAL INFARCTION	PST MU2.5/PST ME2500	P-LT>30	594	2	SAE	NO
CV168022-244-3	47/M	0.790	CEREBROVASCULAR ACCIDENT	MU2.5/ME1500	LT	419	2	AE	NO
			CEREBROVASCULAR ACCIDENT	MU2.5/ME1500	LT	419	2	AE	NO
CV168022-255-8	64/F	1.770	ANGINA UNSTABLE	MU5/ME2500	LT	313	1	AE	NO
CV168022-255-9	54/F	0.320	ANGINA PECTORIS	MU2.5/ME1500	LT	276	2	SAE	NO
CV168022-256-4	61/F	1.690	CORONARY ARTERY ATHEROSCLEROSIS	MU5/ME1500	ST	94	2	SAE	NO
			CORONARY ARTERY ATHEROSCLEROSIS	MU5/ME1500	ST	96	2	AE	NO
			ANGINA PECTORIS	MU5/ME1500	LT	357	3	SAE	NO
CV168022-287-1	52/M	0.980	MYOCARDIAL INFARCTION	MU2.5/ME2000	ST	10	4	SAE	NO

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
Includes events that occurred during the Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168022

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168022-287-1	52/M		CARDIOVASCULAR DEATH	MU2.5/ME2000	ST	10			
CV168022-292-3	62/M	19.460	CORONARY ARTERY DISEASE	PST PLA/PST ME1500	PST ST	171	3	SAE	NO
CV168022-300-4	57/M	3.800	MYOCARDIAL INFARCTION	MU2.5/ME2000	ST	121	3	SAE	YES
CV168022-303-26	66/F	1.810	ANGINA UNSTABLE	MU2.5/ME2000	ST	106	3	SAE	NO

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
Includes events that occurred during the Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168025

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168025-1-9	60/M	7.403	ANGINA PECTORIS	MU5/ME2000	LT	300	2	SAE	NO
CV168025-3-6	56/M	0.482	CORONARY ARTERY DISEASE	PST MU5/PST ME2000	PST LT	305	2	SAE	NO
CV168025-15-6	54/F	3.898	CEREBROVASCULAR ACCIDENT	PI30/ME2500	ST	109	1	SAE	NO
CV168025-47-5	57/M	0.559	ANGINA UNSTABLE	PI30/ME2000	LT	257	4	SAE	NO
CV168025-63-13	46/M	0.925	TRANSIENT ISCHAEMIC ATTACK	MU5/ME2000	LT	255	2	AE	NO
			TRANSIENT ISCHAEMIC ATTACK	MU5/ME2000	LT	255	2	AE	NO
CV168025-68-12	48/F	4.738	ANGINA PECTORIS	PST PI30/PST ME2000	PST ST	57	1	SAE	NO
CV168025-68-22	57/M	1.733	ANGINA PECTORIS	MU5/ME2000	ST	105	1	AE	NO
CV168025-125-1	56/M	1.530	MYOCARDIAL ISCHAEMIA	PI30/ME2000	ST	93	1	AE	NO

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
A * in treatment means event onset was during an interruption of study treatment.
A $ in treatment means event onset was during an interruption of metformin.
Includes events that occurred from the start of Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168025

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168025-166-5	43/M	1.650	CORONARY ARTERY ATHEROSCLEROSIS	MU5/ME1500	ST	8	2	SAE	NO
CV168025-171-2	54/M	16.730	CORONARY ARTERY DISEASE	PI30/ME2000	LT	337	2	SAE	NO
CV168025-184-7	53/F	5.870	MYOCARDIAL ISCHAEMIA	PST PI30/PST ME1500	PST LT	346	1	AE	NO
CV168025-193-9	66/F	5.310	MYOCARDIAL INFARCTION	PST MU5/PST ME2000	PST LT	202	4	SAE	NO
			SUDDEN CARDIAC DEATH	PST MU5/PST ME2000	PST LT	202	4	SAE	NO
			CARDIOVASCULAR DEATH	PST MU5/PST ME2000	PST LT	202			
CV168025-193-10	61/M	3.440	CARDIOVASCULAR DEATH	PST MU5/PST ME2000	PST LT	208			
CV168025-203-3	52/M	6.256	CORONARY ARTERY DISEASE	MU5*/ME2000$	ST	134	3	SAE	NO

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
A * in treatment means event onset was during an interruption of study treatment.
A $ in treatment means event onset was during an interruption of metformin.
Includes events that occurred from the start of Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168025

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168025-206-6	64/M	0.545	CORONARY ARTERY DISEASE	PI30/ME2000	ST	126	2	SAE	NO
CV168025-234-6	65/F	20.540	MYOCARDIAL ISCHAEMIA	MU5/ME2000	ST	129	1	AE	NO
CV168025-235-16	69/M	1.560	ANGINA PECTORIS	PI30/ME1500	LT	270	1	AE	NO
			CORONARY ARTERY DISEASE	PI30/ME1500	LT	270	1	AE	NO
CV168025-236-3	58/F	2.310	CEREBROVASCULAR ACCIDENT	PST MU5/PST ME2000	PST LT	360	3	SAE	NO
CV168025-241-3	67/M	5.930	CARDIOVASCULAR DEATH	PST MU5/PST ME1500	PST ST	144			
CV168025-241-38	60/F	2.880	CEREBROVASCULAR ACCIDENT	MU5/PST ME2000	LT	282	4	SAE	NO
			CARDIOVASCULAR DEATH	PST MU5/PST ME2000	PST LT	292			
CV168025-288-48	51/M	3.980	ANGINA UNSTABLE	MU5/ME2500	ST	27	3	SAE	NO
CV168025-289-64	58/M	1.850	ANGINA PECTORIS	PI30/ME1500	LT	240	1	AE	NO

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
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Includes events that occurred from the start of Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

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Attachment 8.4.6.1A:
Listing of Subjects with Cardiovascular Events During Short-Term Combined with Long-Term Phase
Protocol CV168025

PROTOCOL-SITE-PAT	AGE/ GENDER	BASELINE HS-CRP	PREFERRED TERM	DOSE AT TIME OF Event	PHASE	Onset Day	INTENSITY	SAE AE	DISCON TINUE
CV168025-289-83	47/F	7.560	ANGINA PECTORIS	MU5/ME1500	ST	133	2	AE	NO
CV168025-291-12	37/M	16.280	MYOCARDIAL ISCHAEMIA	PI30/ME2500	LT	168	2	SAE	NO
			SILENT MYOCARDIAL INFARCTION	PI30/ME2500	LT	168	2	SAE	NO
CV168025-314-1	53/M	3.470	CARDIOVASCULAR DEATH	PST MU5/PST ME1500	PST ST	110			

Data set: Treated Subjects
Includes all cardiovascular-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
A * in treatment means event onset was during an interruption of study treatment.
A $ in treatment means event onset was during an interruption of metformin.
Includes events that occurred from the start of Lead-In Phase.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe.
Onset Day: Calculated from start date of Short-Term Phase to Event
For Events of Cardiovascular Death, the intensity, SAE/AE and discontinue will be missing.
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_cvlst.sas MEDDRA VERSION: 8 05AUG05 11:27

Attachment 8.4.7: Subject Listing of All CHF Related Events

12 page(s) excluding cover page

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Attachment 8.4.7:
Subject Listing of All CHF Related Events

SUBJECT (AGE/GENDER/RACE) TREAT AT ONSET:	STUDY PERIOD BETA BLOCKER	ONSET DATE RESOLUTION DATE	DUR TYPE	TREATMENT GROUP/REGIMEN PREFERRED TERM (PT) CRF VERBATIM (VT)	REL INT	TRT ACT
CV168006-34-3 (59/F/1) PST BMS10	PST LT YES	27-APR-04 29-APR-04	3D SAE	BMS 1.5/5/10 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	3 2	1 5
CV168006-36-9 (69/F/1) BMS20	ST NO	23-MAY-02 C	- AE	BMS 20 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	3 1	1 5
	ST NO	23-MAY-02 C	- AE	BMS 20 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	3 1	1 5
	ST NO	23-MAY-02 20-JUN-02	29D AE	BMS 20 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	3 1	1 5

- = Missing
RACE: 1 = WHITE 2 = BLACK/AFRICAN AMER 10 = AMER INDIAN/ALASKA NATIVE 11 = ASIAN
12 = NATIVE HAWAIIAN/PACIFIC ISLANDER 98 = OTHER
ACT (ACTION): 1 = NONE 2 = DOSE REDUCED 3 = DOSE INCREASED 4 = DRUG INTERRUPTED 5 = DRUG DISCONTINUED
REL (RELATIONSHIP): 1 = CERTAIN 2 = PROBABLE 3 = POSSIBLE 4 = UNLIKELY 5 = UNRELATED
INT (INTENSITY): 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE
TRT (TREATMENT REQUIRED): 0 = NO 1 = YES
DUR (DURATION): D = DAYS H = HOURS M = MINUTES

Beta-Blocker use at any time during treatment
CHF terms are based upon the Muraglitazar Predefined List of Events
Includes all events reported from studies CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT

DATASET: Treated Subjects and Open-Label Cohort
MEDDRA VERSION: 8
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_chfbbuse.sas 27JUL05 15:06

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Attachment 8.4.7:
Subject Listing of All CHF Related Events

SUBJECT (AGE/GENDER/RACE) TREAT AT ONSET:	STUDY PERIOD BETA BLOCKER	ONSET DATE RESOLUTION DATE	DUR TYPE	TREATMENT GROUP/REGIMEN PREFERRED TERM (PT) CRF VERBATIM (VT)	REL INT	TRT ACT
CV168006-38-4 (68/M/1) BMS20	LT YES	22-JAN-03 C	- AE	BMS 20 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	4 1	1 1
CV168006-41-2 (63/M/1) PST BMS5	PST LT NO	18-NOV-03 C	- AE	BMS 5 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	4 1	1 1
CV168006-85-1 (61/F/1) BMS5	LT YES	16-DEC-02 08-FEB-03	55D AE	BMS 5 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	3 2	1 1
	LT YES	16-DEC-02 C	- AE	BMS 5 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	3 2	1 5

- = Missing
RACE: 1 = WHITE 2 = BLACK/AFRICAN AMER 10 = AMER INDIAN/ALASKA NATIVE 11 = ASIAN
12 = NATIVE HAWAIIAN/PACIFIC ISLANDER 98 = OTHER
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REL (RELATIONSHIP): 1 = CERTAIN 2 = PROBABLE 3 = POSSIBLE 4 = UNLIKELY 5 = UNRELATED
INT (INTENSITY): 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE
TRT (TREATMENT REQUIRED): 0 = NO 1 = YES
DUR (DURATION): D = DAYS H = HOURS M = MINUTES

Beta-Blocker use at any time during treatment
CHF terms are based upon the Muraglitazar Predefined List of Events
Includes all events reported from studies CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT

DATASET: Treated Subjects and Open-Label Cohort
MEDDRA VERSION: 8
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Attachment 8.4.7:
Subject Listing of All CHF Related Events

SUBJECT (AGE/GENDER/RACE) TREAT AT ONSET:	STUDY PERIOD BETA BLOCKER	ONSET DATE RESOLUTION DATE	DUR TYPE	TREATMENT GROUP/REGIMEN PREFERRED TERM (PT) CRF VERBATIM (VT)	REL INT	TRT ACT
CV168006-85-1 (61/F/1) BMS5	LT YES	16-DEC-02 31-DEC-02	16D AE	BMS 5 PULMONARY OEDEMA PULMONARY EDEMA	3 2	1 5
CV168006-91-1 (51/F/1) BMS10	ST YES	30-APR-02 21-MAY-02	22D AE	BMS 10 CARDIAC FAILURE CONGESTIVE POSS CHF	2 2	0 5
CV168006-101-5 (52/M/1) BMS10	LT YES	08-JUN-04 C	- AE	BMS 10 CARDIAC FAILURE CONGESTIVE PROBABLE CONGESTIVE HEART FAILURE	2 2	1 5
CV168006-114-5 (54/F/1) BMS10	ST YES	04-JUN-02 28-JUN-02	25D AE	BMS 10 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	3 2	0 1

- = Missing
RACE: 1 = WHITE 2 = BLACK/AFRICAN AMER 10 = AMER INDIAN/ALASKA NATIVE 11 = ASIAN
12 = NATIVE HAWAIIAN/PACIFIC ISLANDER 98 = OTHER
ACT (ACTION): 1 = NONE 2 = DOSE REDUCED 3 = DOSE INCREASED 4 = DRUG INTERRUPTED 5 = DRUG DISCONTINUED
REL (RELATIONSHIP): 1 = CERTAIN 2 = PROBABLE 3 = POSSIBLE 4 = UNLIKELY 5 = UNRELATED
INT (INTENSITY): 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE
TRT (TREATMENT REQUIRED): 0 = NO 1 = YES
DUR (DURATION): D = DAYS H = HOURS M = MINUTES

Beta-Blocker use at any time during treatment
CHF terms are based upon the Muraglitazar Predefined List of Events
Includes all events reported from studies CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT

DATASET: Treated Subjects and Open-Label Cohort
MEDDRA VERSION: 8
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_chfbbuse.sas 27JUL05 15:06

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Attachment 8.4.7:
Subject Listing of All CHF Related Events

SUBJECT (AGE/GENDER/RACE) TREAT AT ONSET:	STUDY PERIOD BETA BLOCKER	ONSET DATE RESOLUTION DATE	DUR TYPE	TREATMENT GROUP/REGIMEN PREFERRED TERM (PT) CRF VERBATIM (VT)	REL INT	TRT ACT
CV168006-157-12 (54/M/1) BMS20	LT YES	08-AUG-03 C	- AE	BMS 10/20/10 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	4 3	1 4
	LT YES	08-AUG-03 C	- AE	BMS 10/20/10 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	4 3	1 1
CV168006-163-4 (63/M/1) BMS20	LT NO	02-OCT-03 15-OCT-03	14D SAE	BMS 20 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	3 2	1 5
CV168006-164-6 (62/M/1) BMS20	ST YES	11-JUN-02 13-JUN-02	3D SAE	BMS 20 CARDIAC FAILURE CONGESTIVE CHF EXACERBATION	4 3	1 1

- = Missing
RACE: 1 = WHITE 2 = BLACK/AFRICAN AMER 10 = AMER INDIAN/ALASKA NATIVE 11 = ASIAN
12 = NATIVE HAWAIIAN/PACIFIC ISLANDER 98 = OTHER
ACT (ACTION): 1 = NONE 2 = DOSE REDUCED 3 = DOSE INCREASED 4 = DRUG INTERRUPTED 5 = DRUG DISCONTINUED
REL (RELATIONSHIP): 1 = CERTAIN 2 = PROBABLE 3 = POSSIBLE 4 = UNLIKELY 5 = UNRELATED
INT (INTENSITY): 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE

TRT (TREATMENT REQUIRED): 0 = NO 1 = YES
DUR (DURATION): D = DAYS H = HOURS M = MINUTES

Beta-Blocker use at any time during treatment
CHF terms are based upon the Muraglitazar Predefined List of Events
Includes all events reported from studies CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT

DATASET: Treated Subjects and Open-Label Cohort
MEDDRA VERSION: 8
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_chfbbuse.sas 27JUL05 15:06

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Attachment 8.4.7:
Subject Listing of All CHF Related Events

SUBJECT (AGE/GENDER/RACE) TREAT AT ONSET:	STUDY PERIOD BETA BLOCKER	ONSET DATE RESOLUTION DATE	DUR TYPE	TREATMENT GROUP/REGIMEN PREFERRED TERM (PT) CRF VERBATIM (VT)	REL INT	TRT ACT
CV168006-164-6 (62/M/1) BMS20	LT YES	17-SEP-02 C	- SAE	BMS 20 CARDIAC FAILURE CONGESTIVE CHF EXACERBATION	4 3	1 5
CV168006-226-9 (66/M/1) BMS10	ST NO	12-OCT-02 30-OCT-02	19D AE	BMS 10 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	2 2	1 1
	ST NO	12-OCT-02 C	- AE	BMS 10 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	2 2	1 1
CV168006-245-27 (63/F/98) BMS5	LT NO	02-DEC-04 C	- SAE	BMS 1.5/5/10 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	3 3	1 5

- = Missing
RACE: 1 = WHITE 2 = BLACK/AFRICAN AMER 10 = AMER INDIAN/ALASKA NATIVE 11 = ASIAN
12 = NATIVE HAWAIIAN/PACIFIC ISLANDER 98 = OTHER
ACT (ACTION): 1 = NONE 2 = DOSE REDUCED 3 = DOSE INCREASED 4 = DRUG INTERRUPTED 5 = DRUG DISCONTINUED
REL (RELATIONSHIP): 1 = CERTAIN 2 = PROBABLE 3 = POSSIBLE 4 = UNLIKELY 5 = UNRELATED
INT (INTENSITY): 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE
TRT (TREATMENT REQUIRED): 0 = NO 1 = YES
DUR (DURATION): D = DAYS H = HOURS M = MINUTES

Beta-Blocker use at any time during treatment
CHF terms are based upon the Muraglitazar Predefined List of Events
Includes all events reported from studies CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT

DATASET: Treated Subjects and Open-Label Cohort
MEDDRA VERSION: 8
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_chfbbuse.sas 27JUL05 15:06

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Attachment 8.4.7:
Subject Listing of All CHF Related Events

SUBJECT (AGE/GENDER/RACE) TREAT AT ONSET:	STUDY PERIOD BETA BLOCKER	ONSET DATE RESOLUTION DATE	DUR TYPE	TREATMENT GROUP/REGIMEN PREFERRED TERM (PT) CRF VERBATIM (VT)	REL INT	TRT ACT
CV168006-252-3 (68/F/1) BMS10	ST YES	13-JUN-02 21-JUN-02	9D AE	BMS 10 CARDIAC FAILURE HEART FAILURE	5 1	0 1
	ST YES	11-SEP-02 14-SEP-02	4D AE	BMS 10 CARDIAC FAILURE WORSENING OF HEART FAILURE	5 2	1 1
CV168006-252-3 (68/F/1) PST BMS10	PST LT YES	12-AUG-03 15-AUG-03	4D SAE	BMS 10 CARDIAC FAILURE HEART FAILURE	2 3	1 5
CV168006-280-3 (66/F/1) BMS10	ST YES	31-MAY-02 25-JUN-02	26D AE	BMS 10 CARDIAC FAILURE CONGESTIVE WORSENING OF CONGESTIVE HEART FAILURE	3 3	1 5

- = Missing
RACE: 1 = WHITE 2 = BLACK/AFRICAN AMER 10 = AMER INDIAN/ALASKA NATIVE 11 = ASIAN
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ACT (ACTION): 1 = NONE 2 = DOSE REDUCED 3 = DOSE INCREASED 4 = DRUG INTERRUPTED 5 = DRUG DISCONTINUED
REL (RELATIONSHIP): 1 = CERTAIN 2 = PROBABLE 3 = POSSIBLE 4 = UNLIKELY 5 = UNRELATED
INT (INTENSITY): 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE
TRT (TREATMENT REQUIRED): 0 = NO 1 = YES
DUR (DURATION): D = DAYS H = HOURS M = MINUTES

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CHF terms are based upon the Muraglitazar Predefined List of Events
Includes all events reported from studies CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT

DATASET: Treated Subjects and Open-Label Cohort
MEDDRA VERSION: 8
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_chfbbuse.sas 27JUL05 15:06

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Attachment 8.4.7:
Subject Listing of All CHF Related Events

SUBJECT (AGE/GENDER/RACE) TREAT AT ONSET:	STUDY PERIOD BETA BLOCKER	ONSET DATE RESOLUTION DATE	DUR TYPE	TREATMENT GROUP/REGIMEN PREFERRED TERM (PT) CRF VERBATIM (VT)	REL INT	TRT ACT
CV168006-291-9	LT	28-MAR-03	22D	BMS 20	3	1
(58/M/1)	YES	18-APR-03	SAE	CARDIAC FAILURE	3	4
BMS20				HEART FAILURE		
CV168006-291-9	PST LT	24-MAY-03	4D	BMS 20	3	1
(58/M/1)	YES	27-MAY-03	SAE	CARDIAC FAILURE	3	5
PST BMS20				HEART FAILURE		
CV168006-419-4	PST LT	06-MAY-03	2D	BMS 5	3	1
(70/F/1)	YES	07-MAY-03	SAE	PULMONARY OEDEMA	3	5
PST BMS5				PULMONARY OEDEMA		
CV168021-55-2	LT	15-NOV-04	-	MUR 2.5	3	1
(65/M/1)	NO	C	SAE	CARDIAC FAILURE CONGESTIVE	3	5
MU2.5/GL15				CONGESTIVE HEART FAILURE		

- = Missing
RACE: 1 = WHITE 2 = BLACK/AFRICAN AMER 10 = AMER INDIAN/ALASKA NATIVE 11 = ASIAN
12 = NATIVE HAWAIIAN/PACIFIC ISLANDER 98 = OTHER
ACT (ACTION): 1 = NONE 2 = DOSE REDUCED 3 = DOSE INCREASED 4 = DRUG INTERRUPTED 5 = DRUG DISCONTINUED
REL (RELATIONSHIP): 1 = CERTAIN 2 = PROBABLE 3 = POSSIBLE 4 = UNLIKELY 5 = UNRELATED
INT (INTENSITY): 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE
TRT (TREATMENT REQUIRED): 0 = NO 1 = YES
DUR (DURATION): D = DAYS H = HOURS M = MINUTES

Beta-Blocker use at any time during treatment
CHF terms are based upon the Muraglitazar Predefined List of Events
Includes all events reported from studies CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT

DATASET: Treated Subjects and Open-Label Cohort
MEDDRA VERSION: 8
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_chfbbuse.sas 27JUL05 15:06

PROTOCOL: CV168 FDA AD COM PAGE: 8

Attachment 8.4.7:
Subject Listing of All CHF Related Events

SUBJECT (AGE/GENDER/RACE) TREAT AT ONSET:	STUDY PERIOD BETA BLOCKER	ONSET DATE RESOLUTION DATE	DUR TYPE	TREATMENT GROUP/REGIMEN PREFERRED TERM (PT) CRF VERBATIM (VT)	REL INT	TRT ACT
CV168021-69-1 (67/F/1) MU2.5/GL15	ST NO	07-DEC-03 08-DEC-03	2D SAE	MUR 2.5 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	4 1	1 5
CV168021-209-10 (47/F/1) MU2.5/GL10	LT NO	23-NOV-04 C	- AE	MUR 2.5 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	5 2	1 5
CV168021-237-5 (56/F/1) PST MU5/PST GL10	PST LT NO	12-SEP-04 22-SEP-04	11D SAE	MUR 5 CARDIAC FAILURE ACUTE SEVERE ACUTE HEART FAILURE	5 4	1 1

- = Missing
RACE: 1 = WHITE 2 = BLACK/AFRICAN AMER 10 = AMER INDIAN/ALASKA NATIVE 11 = ASIAN
12 = NATIVE HAWAIIAN/PACIFIC ISLANDER 98 = OTHER
ACT (ACTION): 1 = NONE 2 = DOSE REDUCED 3 = DOSE INCREASED 4 = DRUG INTERRUPTED 5 = DRUG DISCONTINUED
REL (RELATIONSHIP): 1 = CERTAIN 2 = PROBABLE 3 = POSSIBLE 4 = UNLIKELY 5 = UNRELATED
INT (INTENSITY): 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE
TRT (TREATMENT REQUIRED): 0 = NO 1 = YES
DUR (DURATION): D = DAYS H = HOURS M = MINUTES

Beta-Blocker use at any time during treatment
CHF terms are based upon the Muraglitazar Predefined List of Events
Includes all events reported from studies CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT

DATASET: Treated Subjects and Open-Label Cohort
MEDDRA VERSION: 8
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_chfbbuse.sas 27JUL05 15:06

PROTOCOL: CV168 FDA AD COM PAGE: 9

Attachment 8.4.7:
Subject Listing of All CHF Related Events

SUBJECT (AGE/GENDER/RACE) TREAT AT ONSET:	STUDY PERIOD BETA BLOCKER	ONSET DATE RESOLUTION DATE	DUR TYPE	TREATMENT GROUP/REGIMEN PREFERRED TERM (PT) CRF VERBATIM (VT)	REL INT	TRT ACT
CV168021-244-14 (55/M/1) MU5/GL15	LT YES	03-MAR-05 06-APR-05	35D SAE	MUR 5 CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE, FUNCTIONAL CLASS II (NYHA)	3 3	1 5
CV168021-301-5 (60/F/1) MU5/GL15	ST YES	14-MAR-04 C	- AE	MUR 5 CARDIAC FAILURE CONGESTIVE POSSIBLE CHF	3 2	1 1
	ST YES	14-MAR-04 05-MAY-04	53D AE	MUR 5 CARDIAC FAILURE CONGESTIVE POSSIBLE CHF	3 2	1 1
	ST YES	05-MAY-04 C	- AE	MUR 5 CARDIAC FAILURE CONGESTIVE POSSIBLE DIASTOLIC CHF	3 1	0 5

- = Missing
RACE: 1 = WHITE 2 = BLACK/AFRICAN AMER 10 = AMER INDIAN/ALASKA NATIVE 11 = ASIAN
12 = NATIVE HAWAIIAN/PACIFIC ISLANDER 98 = OTHER
ACT (ACTION): 1 = NONE 2 = DOSE REDUCED 3 = DOSE INCREASED 4 = DRUG INTERRUPTED 5 = DRUG DISCONTINUED
REL (RELATIONSHIP): 1 = CERTAIN 2 = PROBABLE 3 = POSSIBLE 4 = UNLIKELY 5 = UNRELATED
INT (INTENSITY): 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE
TRT (TREATMENT REQUIRED): 0 = NO 1 = YES
DUR (DURATION): D = DAYS H = HOURS M = MINUTES

Beta-Blocker use at any time during treatment
CHF terms are based upon the Muraglitazar Predefined List of Events
Includes all events reported from studies CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT

DATASET: Treated Subjects and Open-Label Cohort
MEDDRA VERSION: 8
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_chfbbuse.sas 27JUL05 15:06

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Attachment 8.4.7:
Subject Listing of All CHF Related Events

SUBJECT (AGE/GENDER/RACE) TREAT AT ONSET:	STUDY PERIOD BETA BLOCKER	ONSET DATE RESOLUTION DATE	DUR TYPE	TREATMENT GROUP/REGIMEN PREFERRED TERM (PT) CRF VERBATIM (VT)	REL INT	TRT ACT
CV168022-153-2	ST	21-FEB-04	2D	MUR 5	2	1
(54/M/1) MU5/ME2000	YES	22-FEB-04	SAE	CARDIAC FAILURE CONGESTIVE ACUTE CHF	2	5
CV168022-255-11	PST LT	19-MAY-04	2D	MUR 2.5	3	1
(63/F/1) PST MU2.5/PST ME2500	NO	20-MAY-04	AE	CARDIAC FAILURE CARDIAC HEART FAILURE	3	5
CV168025-45-5	ST	13-APR-04	7D	BMS-298585 5 mg	3	1
(59/F/2) MU5/ME2000	YES	19-APR-04	AE	CARDIAC FAILURE CONGESTIVE CHF	2	5

- = Missing
RACE: 1 = WHITE 2 = BLACK/AFRICAN AMER 10 = AMER INDIAN/ALASKA NATIVE 11 = ASIAN
12 = NATIVE HAWAIIAN/PACIFIC ISLANDER 98 = OTHER
ACT (ACTION): 1 = NONE 2 = DOSE REDUCED 3 = DOSE INCREASED 4 = DRUG INTERRUPTED 5 = DRUG DISCONTINUED
REL (RELATIONSHIP): 1 = CERTAIN 2 = PROBABLE 3 = POSSIBLE 4 = UNLIKELY 5 = UNRELATED
INT (INTENSITY): 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE
TRT (TREATMENT REQUIRED): 0 = NO 1 = YES
DUR (DURATION): D = DAYS H = HOURS M = MINUTES

Beta-Blocker use at any time during treatment
CHF terms are based upon the Muraglitazar Predefined List of Events
Includes all events reported from studies CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT

DATASET: Treated Subjects and Open-Label Cohort
MEDDRA VERSION: 8
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_chfbbuse.sas 27JUL05 15:06

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Attachment 8.4.7:
Subject Listing of All CHF Related Events

SUBJECT (AGE/GENDER/RACE) TREAT AT ONSET:	STUDY PERIOD BETA BLOCKER	ONSET DATE RESOLUTION DATE	DUR TYPE	TREATMENT GROUP/REGIMEN PREFERRED TERM (PT) CRF VERBATIM (VT)	REL INT	TRT ACT
CV168025-48-6 (63/M/1) MU5/ME2000	ST YES	01-MAR-04 05-MAR-04	5D SAE	BMS-298585 5 mg CARDIAC FAILURE HEART FAILURE	5 1	1 1
CV168025-193-9 (66/F/1) MU5/PST ME2000	LT YES	02-OCT-04 C	- SAE	BMS-298585 5 mg CARDIAC FAILURE PUMP FAILURE	5 4	0 1
CV168025-235-3 (61/F/1) PST MU5/PST ME1500	PST LT NO	22-SEP-04 07-OCT-04	16D SAE	BMS-298585 5 mg CARDIAC FAILURE HEART FAILURE NYHA II	3 2	1 5

- = Missing
RACE: 1 = WHITE 2 = BLACK/AFRICAN AMER 10 = AMER INDIAN/ALASKA NATIVE 11 = ASIAN
12 = NATIVE HAWAIIAN/PACIFIC ISLANDER 98 = OTHER
ACT (ACTION): 1 = NONE 2 = DOSE REDUCED 3 = DOSE INCREASED 4 = DRUG INTERRUPTED 5 = DRUG DISCONTINUED
REL (RELATIONSHIP): 1 = CERTAIN 2 = PROBABLE 3 = POSSIBLE 4 = UNLIKELY 5 = UNRELATED
INT (INTENSITY): 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE
TRT (TREATMENT REQUIRED): 0 = NO 1 = YES
DUR (DURATION): D = DAYS H = HOURS M = MINUTES

Beta-Blocker use at any time during treatment
CHF terms are based upon the Muraglitazar Predefined List of Events
Includes all events reported from studies CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT

DATASET: Treated Subjects and Open-Label Cohort
MEDDRA VERSION: 8
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_chfbbuse.sas 27JUL05 15:06

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Attachment 8.4.7:
Subject Listing of All CHF Related Events

SUBJECT (AGE/GENDER/RACE) TREAT AT ONSET:	STUDY PERIOD BETA BLOCKER	ONSET DATE RESOLUTION DATE	DUR TYPE	TREATMENT GROUP/REGIMEN PREFERRED TERM (PT) CRF VERBATIM (VT)	REL INT	TRT ACT
CV168025-236-7 (57/F/1) PST MU5/ME2000	PST ST NO	27-MAY-04 11-JUN-04	16D SAE	BMS-298585 5 mg CARDIAC FAILURE CONGESTIVE CHF III (NYHA)	4 2	1 5
CV168025-289-74 (63/M/1) PI30/ME1500	LT YES	10-NOV-04 18-NOV-04	9D SAE	Pioglitazone 30 mg CARDIAC FAILURE CONGESTIVE CONGESTIVE HEART FAILURE	3 3	1 5
CV168025-337-5 (61/M/1) PI30/ME2500	ST YES	01-JUL-04 04-OCT-04	96D AE	Pioglitazone 30 mg CARDIAC FAILURE CONGESTIVE MILD CHF	3 1	1 5

- = Missing
RACE: 1 = WHITE 2 = BLACK/AFRICAN AMER 10 = AMER INDIAN/ALASKA NATIVE 11 = ASIAN
12 = NATIVE HAWAIIAN/PACIFIC ISLANDER 98 = OTHER
ACT (ACTION): 1 = NONE 2 = DOSE REDUCED 3 = DOSE INCREASED 4 = DRUG INTERRUPTED 5 = DRUG DISCONTINUED
REL (RELATIONSHIP): 1 = CERTAIN 2 = PROBABLE 3 = POSSIBLE 4 = UNLIKELY 5 = UNRELATED
INT (INTENSITY): 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE
TRT (TREATMENT REQUIRED): 0 = NO 1 = YES
DUR (DURATION): D = DAYS H = HOURS M = MINUTES

Beta-Blocker use at any time during treatment
CHF terms are based upon the Muraglitazar Predefined List of Events
Includes all events reported from studies CV168006 ST+LT, CV168018 including OL cohort, CV168021 ST+LT, CV168022 ST+LT and CV168025 ST+LT

DATASET: Treated Subjects and Open-Label Cohort
MEDDRA VERSION: 8
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/fda_adv/dev/cpp/aes_chfbbuse.sas 27JUL05 15:06

Attachment 8.4.7.1: Listing of All Reported AEs of Heart Failure, Muraglitazar 10 and 20 mg in Study CV168006

2 page(s) excluding cover page

Attachment 8.4.7.1: Listing of All Reported AEs of Heart Failure, Muraglitazar 10 and 20 mg in Study CV168006

	SUBJECT ID	AGE/ GENDER	DOSE AT TIME OF ONSET	PHASE	DAYS SINCE FIRST DOSE	INTENSITY	SAE AE	RESOLVED	DISCONTINUATION
Any Mur	CV168006-34-3	59/F	PST BMS10	PST LT	868	2	SAE	YES	YES
	CV168006-36-9	69/F	BMS20	ST	24	1	AE	C	YES
						1	AE	C	YES
						1	AE	YES	YES
	CV168006-38-4	68/M	BMS20	LT	351	1	AE	C	NO
	CV168006-91-1	51/F	BMS10	ST	117	2	AE	YES	YES
	CV168006-114-5	54/F	BMS10	ST	62	2	AE	YES	NO
	CV168006-157-12	54/M	BMS20	LT	506	3	AE	C	NO
						3	AE	C	NO
	CV168006-163-4	63/M	BMS20	LT	557	2	SAE	YES	YES
	CV168006-164-6	62/M	BMS20	LT	190	3	SAE	C	YES
				ST	92	3	SAE	YES	NO

Attachment 8.4.7.1: Listing of All Reported AEs of Heart Failure, Muraglitazar 10 and 20 mg in Study CV168006

SUBJECT ID	AGE/ GENDER	DOSE AT TIME OF ONSET	PHASE	DAYS SINCE FIRST DOSE	INTENSITY	SAE AE	RESOLVED	DISCONTINUATION
CV168006-226-9	66/M	BMS10	ST	150	2	AE	YES	NO
					2	AE	C	NO
CV168006-252-3	68/F	BMS10	ST	50	1	AE	YES	NO
				140	2	AE	YES	NO
		PST BMS10	PST LT	475	3	SAE	YES	YES
CV168006-291-9	58/M	BMS20	LT	390	3	SAE	YES	NO
		PST BMS20	PST LT	447	3	SAE	YES	YES

Data set: Treated Subjects
Includes all CHF-related terms based upon the muraglitazar predefined list of events. Duplicate events are printed.
Non-serious events up to last treatment date included.
Serious events up to 30 days post treatment included.
INTENSITY:1 = mild 2 = moderate 3 = severe 4 = very severe. RESOLVED: C=continuing
PROGRAM SOURCE: /wwbdm/clin/proj/cv/168/iss_ise/dev/cpp/aes_chflst.sas MEDDRA VERSION: 7 04NOV04 12:18

Attachment 8.4.7.2: Listing of Predefined Terms for the Heart Failure Adjudication Committee

1 page(s) excluding cover page

ATTACHMENT 8.4.7.2: LISTING OF PREDEFINED TERMS FOR THE HEART FAILURE ADJUDICATION COMMITTEE

Listing of predefined Preferred Terms (as found in MedDRA 7.0) used to determine the cases that were submitted to the Adjudication Committee for evaluation of heart failure:

Cardiac failure	Dyspnoea at rest
Cardiac failure acute	Dyspnoea exacerbated
Cardiac failure chronic	Dyspnoea exertional
Cardiac failure congestive	Dyspnoea
Cardiac failure high output	Dyspnoea paroxysmal nocturnal
Cardiogenic shock	Nocturnal dyspnoea
Pulmonary congestion	Orthopnoea
Pulmonary oedema	Tachypnoea
Acute pulmonary oedema	Cardiac asthma
Left ventricular failure	Hepatic congestion
Right ventricular failure	Hepatojugluar reflux
Acute pre-renal failure	Ventricular failure
Low cardiac output syndrome	Cardiopulmonary failure
Acute left ventricular failure	Chronic left ventricular failure
Acute right ventricular failure	Chronic right ventricular failure

Attachment 8.5.3.2A: Mean Change from Baseline in Hematologic Parameters at Week 24, Muraglitazar up to 5 mg

1 page(s) excluding cover page

Attachment 8.5.3.2A: Mean Change from Baseline in Hematologic Parameters at Week 24, Muraglitazar up to 5 mg

	Non-titrated Dose			Initial or Titrated Dose		
Parameter	MUR 1.5 N= 177	Any MUR 2.5 N= 535	Any MUR 5 N=1296	Any MUR =<5 N=2374	Any PLA * N= 528	Any PIO =<45 N= 823
Hemoglobin (g/dL)						
n	137	437	1097	1850	359	624
Baseline Mean (SD)	14.52 (1.25)	14.44 (1.42)	14.39 (1.28)	14.42 (1.32)	14.42 (1.30)	14.36 (1.23)
Mean Change from Baseline (SE)	-0.25 (0.06)	-0.24 (0.04)	-0.57 (0.02)	-0.44 (0.02)	-0.03 (0.04)	-0.47 (0.03)
Hematocrit (%)						
n	137	435	1091	1841	354	611
Baseline Mean (SD)	44.65 (3.97)	44.89 (4.47)	43.99 (4.02)	44.29 (4.16)	44.84 (4.03)	43.40 (3.66)
Mean Change from Baseline (SE)	-0.04 (0.20)	-1.19 (0.14)	-0.89 (0.08)	-0.77 (0.07)	-0.78 (0.14)	0.12 (0.11)
Leukocytes (x 10^3 c/uL)						
n	137	437	1097	1850	359	624
Baseline Mean (SD)	6.67 (1.80)	6.77 (1.85)	6.74 (1.94)	6.73 (1.91)	6.67 (1.76)	6.66 (1.73)
Mean Change from Baseline (SE)	-0.05 (0.12)	-0.21 (0.06)	-0.36 (0.04)	-0.30 (0.03)	0.05 (0.07)	-0.08 (0.05)
Neutrophils (absolute) (x 10^3 c/uL)						
n	137	436	1086	1838	357	620
Baseline Mean (SD)	3.99 (1.41)	4.01 (1.45)	4.01 (1.37)	4.00 (1.40)	4.00 (1.42)	3.93 (1.37)
Mean Change from Baseline (SE)	-0.10 (0.11)	-0.16 (0.05)	-0.28 (0.03)	-0.24 (0.03)	-0.02 (0.07)	-0.02 (0.05)

Dataset: Treated Subjects
* Includes background therapy with secondary medication.
Note: Dose titration was permitted during the rescue period of th ST double-blind phase.
Includes CV168006, CV168018 excluding OL cohort, CV168021, CV168022 and CV168025.

PROGRAM SOURCE: /wwBDM/CLIN/PROJ/CV/168/ISS_ISE/DEV/STATS/LAB_MEAN_ST2.SAS

Attachment 8.5.3.2B: Mean (SD) Change from Baseline in Hematologic Parameters at Week 104, LT Monotherapy

1 page(s) excluding cover page

Attachment 8.5.3.2B: Mean (SD) Change from Baseline in Hematologic Parameters at Week 104, LT Monotherapy

Parameter	Initial or Titrated	
	Any Mur ≤ 5 N = 283	**Any Pio ≤ 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/μL)	-0.28 (1.34)	-0.19 (1.79)
ANC (x 10^3 cells/μL)	-0.30 (1.16)	-0.19 (1.66)

Source: Appendix 3.1B of SCS

Attachment 8.5.4: Frequency of Hypoglycemic Events, Subjects with Type 2 Diabetes, (NDA Data Set)

1 page(s) excluding cover page

Attachment 8.5.4: Frequency of Hypoglycemic Events, Subjects with Type 2 Diabetes, (NDA Data Set)

Study		N	Number of Events	Number (%) of Subjects
ST Monotherapy				
CV168006*	MUR 1.5	259	0	0
	MUR 5	245	2	2 (0.8)
	PIO 15	251	0	0
CV168018	MUR 2.5	111	0	0
	MUR 5	114	0	0
	PLA	115	0	0
All	MUR 5	359	2	2 (0.6)
CV168018	MUR 5 OL	109	0	0
Combination with SU				
CV168021	MUR 2.5+GLY	191	19	14 (7.3)
	MUR 5+GLY	193	28	20 (10.4)
	PLA+GLY	199	20	10 (5.0)
Combination with MET				
CV168022	MUR 2.5+MET	233	0	0
	MUR 5+MET	205	0	0
	PLA+MET	214	9	1 (0.5)
CV168025	MUR 5+MET	587	3	3 (0.5)
	PIO 30+MET	572	1	1 (0.2)
All	MUR 5+MET	792	3	3 (0.4)
LT Monotherapy, CV168006				
Non-titrated Dose:				
	MUR 1.5	75	1	1 (1.3)
	MUR 5	108	0	0
Initial or Titrated Dose:**				
	ANY MUR <= 5	459	6	5 (1.1)
	ANY PIO <= 45	146	2	2 (1.4)

N = number of Treated or Open-Label Cohort Subjects
* Prior to Rescue
**Dose titration was permitted during rescue period of ST phase & LT double-blind extension for CV168006. Subjects who started with 0.5, 1.5 or 5 mg dose & had titration to 10 mg or higher dose of muraglitazar will have data included up to & including 5mg dose.
DATA SET: Treated Subjects and Open-Label Cohort
MEDDRA VERSION: 7
ROGRAM SOURCE: /wwbdm/clin/proj/cv/168/iss_ise/dev/cpp/aes_hypo.sas 29NOV04 11:57

Attachment 8.5.5: Subjects with Creatinine Greater Than 1.8 mg/dL (Dose-Ranging Study CV168006)

1 page(s) excluding cover page

Attachment 8.5.5: Subjects with Creatinine Greater Than 1.8 mg/dL (Dose-Ranging Study CV168006)

	Muraglitazar					Pioglitazone
	0.5 mg	**1.5 mg**	**5 mg**	**10 mg**	**20 mg**	**15 mg**
Total # Subjects with Data	233	256	242	245	237	247
Creatinine > 1.8 mg/dL (%)	3 (1.3)	3 (1.2)	2 (0.8)	1 (0.4)	5 (2.1)	2 (0.8)

Attachment 8.5.6.1A: Mean Change from Baseline in Liver Function Parameters at Week 24, Muraglitazar up to 5 mg

1 page(s) excluding cover page

Attachment 8.5.6.1A: Mean Change from Baseline in Liver Function Parameters at Week 24, Muraglitazar up to 5 mg

Parameter	Non-titrated Dose			Initial or Titrated Dose		
	MUR 1.5 N= 177	Any MUR 2.5 N= 535	Any MUR 5 N=1296	Any MUR =<5 * N=2374	Any PLA * N= 528	Any PIO =<45 * N= 823
ALT (U/L)						
n	139	442	1118	1880	364	631
Baseline Mean (SD)	28.91 (12.48)	30.30 (14.98)	30.15 (14.79)	30.18 (14.56)	31.03 (18.00)	32.26 (16.06)
Mean Change from Baseline (SE)	-3.83 (0.94)	-3.45 (1.29)	-7.96 (0.36)	-6.40 (0.39)	-0.83 (0.88)	-7.70 (0.93)
AST (U/L)						
n	139	442	1118	1880	364	631
Baseline Mean (SD)	23.67 (8.38)	23.91 (10.68)	22.86 (9.36)	23.34 (9.70)	25.09 (17.42)	23.48 (10.24)
Mean Change from Baseline (SE)	-1.85 (0.54)	-1.24 (0.90)	-2.27 (0.25)	-2.03 (0.27)	-0.62 (0.93)	-1.14 (1.13)
Total Bilirubin (mg/dL)						
n	139	442	1117	1879	363	631
Baseline Mean (SD)	0.53 (0.25)	0.55 (0.28)	0.54 (0.24)	0.55 (0.25)	0.56 (0.30)	0.53 (0.27)
Mean Change from Baseline (SE)	0.00 (0.02)	-0.03 (0.01)	-0.05 (0.01)	-0.04 (0.00)	0.00 (0.01)	-0.02 (0.01)

Dataset: Treated Subjects
* Includes background therapy with secondary medication.
Note: Dose titration was permitted during the rescue period of the ST double-blind phase.
Includes CV168006, CV168018 excluding OL cohort, CV168021, CV168022 and CV168025.

PROGRAM SOURCE: /WWBDM/CLIN/PROJ/CV/168/ISS_ISE/DEV/STATS/LAB_MEAN_ST2.SAS 19-OCT-2004 11:31

Attachment 8.5.6.1B: Mean (SD) Change from Baseline in Liver Function Parameters at Week 104, LT Monotherapy

1 page(s) excluding cover page

Attachment 8.5.6.1B: Mean (SD) Change from Baseline in Liver Function Parameters at Week 104, LT Monotherapy

Parameter	Initial or Titrated	
	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)

Source: Appendix 3.1B from SCS