

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #: 21865 APPLICATION TYPE: NDA.....
SPONSOR: BMS PROPRIETARY NAME: Muraglitazar.....
CATEGORY OF DRUG: Antidiabetic USAN / Established Name:
ROUTE: Oral.....
MEDICAL REVIEWER: Robert I Misbin.. REVIEW DATE: 7/29/05

SUBMISSIONS REVIEWED IN THIS DOCUMENT

| Document Date: | CDER Stamp Date: | Submission Type: | Comments: |
|----------------|------------------|-----------------------|-----------|
| 12/17/04 | | NDA | |
| 7/22/05 | | Response to questions | |

Briefing Document for Advisory Committee – Review of Efficacy

Signed: Medical Reviewer: Robert I Misbin MD Date: 8/05/05

Medical Team Leader: _____ Date: _____

4.5 Compliance with Good Clinical Practices:

The trials were conducted in accordance with high ethical standards. In contrast to what has often been done in the past, diabetes drugs were not discontinued in order to make patients eligible for randomization. It is note worthy that glucose levels tended to fall even in patients on placebo. This is because of withdrawal criteria that prevented deterioration of glycemic control in patients who received ineffective therapy. Particularly commendable is the use of low dose Muraglitazar, instead of placebo, as the basis of comparison in study 006.

6.1 Indication:

Type 2 Diabetes

6.1.1 Methods:

Five randomized double blind trials were reviewed.

6.1.2 Endpoints

The primary endpoint was change in HbA1c.

6.1.3 Study design

Five trials were conducted to evaluate the use of MURAGLITAZAR in patients with type 2 diabetes. They were double-blind randomized trials lasting 24 weeks, plus extensions. The primary measure of efficacy was change in HbA1c from baseline to 24 weeks. Entry criteria and dosing regimens were appropriate. Key inclusion criteria were HbA1c between 7% and 10%, and BMI less than or equal to 41 kg/m² and fasting C peptide > 1.5 ng/mL. Key exclusion criteria were NYCA Class 111 or 1V heart failure and current use of fibrates. Although the change in HbA1c was determined at 24 weeks, the changes in lipids were determined at 12 weeks. This allowed addition of lipid-lowering agents beyond week 12 when clinically appropriate. Subjects on statins were not excluded but the dose of statin could not be changed during the first 12 weeks. Niacin, bile-acid binding agents, and statin/fibrate combinations were excluded.

6.1.4 Efficacy Findings

Monotherapy

Two 24-week, randomized, double blind, controlled, monotherapy studies were conducted to evaluate the use of MURAGLITAZAR in patients with type 2 diabetes.

Study 018 : Placebo-Controlled Monotherapy Study

This was a 24-week randomized double blind study of patients with type 2 diabetes not taking other antidiabetic therapy. Patients with a baseline A1C of 7-10% were randomized to one of three treatment arms (MURAGLITAZAR 2.5 mg or 5 mg, or placebo once daily). In an open-label cohort within the same study, patients with a baseline A1C of 10-12% (mean 10.7%) were treated for 24 weeks with MURAGLITAZAR, 5 mg once daily. Patients were withdrawn from open-label treatment based on the following criteria:

Prespecified Glycemic Control Criteria for Discontinuation from the Open-label Treatment Cohort

| Visit - Open-label (Period D) | Subjects with screening HbA _{1c} >10.0% and ≤11.0% | Subjects with screening HbA _{1c} > 11.0% and ≤12.0% |
|-------------------------------|---|--|
| Week 6 - FPG value | <20 mg/dL (1.1 mmol/L) decline | <30 mg/dL (1.7 mmol/L) decline |
| Week 8 - FPG value | <40 mg/dL (2.2 mmol/L) decline | <50 mg/dL (2.8 mmol/L) decline |
| Weeks 12,16,20 - FPG value | <60 mg/dL (3.3 mmol/L) decline | <70 mg/dL (3.9 mmol/L) decline |

(Glycemic control was based on the decline in FPG from the enrollment visit)

Demographic characteristics of patients at baseline are shown in the following table:

Demographic and Baseline Characteristics, Randomized Subjects and Open-label Cohort

| Characteristic | Muraglitazar 2.5 mg N=111 | Muraglitazar 5 mg N=114 | Placebo N=115 | Muraglitazar 5 mg open-label N=109 |
|--------------------------------------|---------------------------------|-------------------------------|------------------|--|
| Age, years Mean (SD) | 52.1 (10.6) | 52.8 (9.7) | 50.4 (10.0) | 50.0 (9.7) |
| Gender, n (%) | | | | |
| Male | 65 (58.6) | 61 (53.5) | 53 (46.1) | 56 (51.4) |
| Female | 46 (41.4) | 53 (46.5) | 62 (53.9) | 53 (48.6) |
| Race, n (%) | | | | |
| White | 89 (80.2) | 90 (78.9) | 86 (74.8) | 75 (68.8) |
| Black | 6 (5.4) | 6 (5.3) | 7 (6.1) | 14 (12.8) |
| Other | 16 (14.4) | 18 (15.8) | 22 (19.1) | 20 (18.3) |
| BMI (kg/m ²) Mean(SD) | 31.5 (5.1) | 31.2 (5.2) | 31.5 (5.7) | 30.2 (5.1) |
| HbA _{1c} (%) Mean (SD) | 8.0 (1.0) | 7.9 (1.0) | 8.0 (1.0) | 10.6 (0.8) |

Compared to placebo, MURAGLITAZAR showed a clinically significant improvement in glycemic control as measured by A1C and FPG (see **Table**).

| Glycemic and Related Parameters in Placebo-Controlled Monotherapy Study at Week 24 | | | |
|---|----------------|---------------------|-------------|
| | Placebo | MURAGLITAZAR | |
| | | 2.5 mg | 5 mg |
| | N=111 | N=105 | N=110 |
| A1C (%) | | | |
| Baseline (mean) | 8.0 | 8.0 | 7.9 |
| Mean change from baseline | -0.3 | -1.0* | -1.2* |
| % patients with final A1C <7% | 30% | 58% | 72% |
| FPG (mg/dL) | | | |
| Baseline (mean) | 162 | 168 | 170 |
| Mean change from baseline | 1 | -26* | -33* |
| Fasting Insulin (µU/ml) | | | |
| Baseline (mean) | 15.6 | 18.4 | 13.6 |
| Mean change from baseline | 0.9 | -2.8 | -3.1 |
| Fasting C-peptide (ng/mL) | | | |
| Baseline (mean) | 3.3 | 3.3 | 3.2 |
| Mean change from baseline | -0.3 | -0.5 | -0.8 |
| Free Fatty Acids (mEq/L) | | | |
| Baseline (mean) | 0.7 | 0.7 | 0.7 |
| Mean % change from baseline | -9% | -19% | -31% |

*p<0.0001 vs. placebo

In the open-label study of patients with a baseline A1C of 10-12% (mean 10.7%) 24 weeks with MURAGLITAZAR 5 mg, there was a mean change from baseline in A1C of -2.6% units and a mean change from baseline in FPG of -68 mg/dl. 62/109 patients (57%) completed 24 weeks of open-label treatment and had a mean change from baseline in A1C of -3.5%.

Body Weight:

The mean change from baseline at Week 24 (LOCF) for body weight was 1.05 kg in the muraglitazar 2.5 mg group, 2.10 kg in the muraglitazar 5 mg group and -0.78 kg in the placebo group. In the open-label cohort there was a mean change from baseline in body weight of 2.9 kg at Week 24 (LOCF).

Lipids:

At Week 12, MURAGLITAZAR 2.5 mg and 5 mg produced greater decreases in TG and greater increases in HDL-C than placebo (see table).

**Lipid Parameters in Placebo-Controlled Monotherapy
Study at Week 12**

| | Placebo | MURAGLITAZAR | |
|------------------------------|---------|--------------|-------|
| | | 2.5 mg | 5 mg |
| | N=114 | N=111 | N=112 |
| Triglycerides (mg/dl) | | | |
| Baseline (mean) | 187 | 193 | 194 |
| Mean % change from baseline | -2% | -18%* | -27%* |
| HDL-C (mg/dL) | | | |
| Baseline (mean) | 45 | 44 | 42 |
| Mean % change from baseline | 2% | 10%** | 16%** |
| ApoB (mg/dL) | | | |
| Baseline (mean) | 104 | 103 | 102 |
| Mean % change from baseline | 0% | -7% | -12% |
| LDL-C (mg/dL) | | | |
| Baseline (mean) | 132 | 130 | 124 |
| Mean % change from baseline | 1% | -1% | -1% |
| Non-HDL-C (mg/dL) | | | |
| Baseline (mean) | 157 | 156 | 151 |
| Mean % change from baseline | 1% | -3% | -5% |

* p<0.0001 vs. placebo

**nominal p-value <0.0001 vs. placebo

Trial 006: Dose-Ranging Monotherapy Study and long-term extension phase:

In a 24-week dose-ranging randomized, double blind study, patients with type 2 diabetes were randomized to receive 0.5 mg, 1.5 mg, 5 mg, 10 mg and 20 mg of MURAGLITAZAR or Pioglitazone 15 mg once daily.

Patients had not received previous antidiabetic therapy, or had not received antidiabetic therapy more than three consecutive days or seven non-consecutive days for the four-six weeks prior to screening. A distant history of gestational diabetes with insulin treatment was not a disqualification. HbA1c at screening was between 7 and 10%. Subjects had a BMI < 41 and serum triglyceride < 600 mg/dl.

During the 24-week double-blind study, patients who failed to achieve adequate glycemic control were “rescued” by going to the next highest dose of study drug. Patients on 0.5 and 1.5 mg went to 5 mg. Patients on 5 mg of MUR went to 10 mg, etc. Patients on 15 mg PIO went to 45 mg. Rescue was based on self-reporting of finger stick glucose determined 4x/day, three to five days before the specified study visit. Criteria for rescue were:

| Visit-Period B | MDG |
|-----------------------|----------------------------|
| Week 6 | > 240 mg/dL (13.32 mmol/L) |
| Week 8 | > 220 mg/dL (12.21 mmol/L) |
| Week 12 | > 200 mg/dL (11.1 mmol/L) |
| Week 16 | > 180 mg/dL (9.99 mmol/L) |
| Week 20 | > 180 mg/dL (9.99 mmol/L) |

Mean age of patients about 54 years in all arms. Other baseline characteristics are shown in the following table:

| Characteristic | 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 |
| Gender, n (%) | | | | | | |
| Male | 131 (56) | 146 (56) | 145 (59) | 128 (51) | 142 (60) | 145 (58) |
| Female | 105 (44) | 113 (44) | 100 (41) | 121 (49) | 95 (40) | 106 (42) |
| Race, n (%) | | | | | | |
| White | 188 (80) | 209 (81) | 207 (84) | 203 (82) | 193 (81) | 204 (81) |
| Black | 16 (7) | 19 (7) | 15 (6) | 16 (6) | 12 (5) | 19 (8) |
| Other | 32 (14) | 31 (12) | 23 (9) | 30 (12) | 32 (14) | 28 (11) |
| BMI (kg/m ²) | | | | | | |
| Mean (SD) | 30.67 (4.90) | 31.16 (4.71) | 30.98 (4.87) | 31.05 (4.67) | 31.36 (4.58) | 31.57 (4.53) |
| HbA _{1c} (%) | | | | | | |
| n | 235 | 258 | 244 | 249 | 237 | 250 |
| Mean (SD) | 8.26 (1.13) | 8.20 (1.08) | 8.25 (1.04) | 8.18 (1.06) | 8.18 (1.12) | 8.36 (1.14) |

Mean change in HbA_{1c} at week 24 is shown in the following table. Mean HbA_{1c} fell in all groups, including 0.5 mg MUR. All higher doses of MUR were superior to 0.5 mg MUR. Mean change for PIO 15 mg was -0.57% units (not shown in table). This is the same result as for MUR 1.5 mg

Primary Efficacy Endpoint: Hemoglobin A_{1c} Change from Baseline at Week 24 (LOCF)

| HbA _{1c} measurement (%) | BMS-298585 | | | | |
|--|-----------------|---------------------|-----------------------|-----------------------|-----------------------|
| | 0.5 mg N=236 | 1.5 mg N=259 | 5 mg N=245 | 10 mg N=249 | 20 mg N=237 |
| 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) |
| Adjusted Mean Change from Baseline (SE) | -0.25 (0.08) | -0.57 (0.07) | -1.18 (0.07) | -1.52 (0.07) | -1.76 (0.07) |
| Each dose relative to lowest dose of BMS-298585 | | | | | |
| Difference in Adjusted Mean Change from Baseline (SE) ^a | - | -0.31 (0.10) | -0.92 (0.11) | -1.27 (0.11) | -1.51 (0.11) |
| 95% two-sided CI | - | (-0.52, -0.11) | (-1.13, -0.72) | (-1.47, -1.06) | (-1.71, -1.30) |
| p-value ^b | - | 0.0008 ^c | < 0.0001 ^c | < 0.0001 ^c | < 0.0001 ^c |

As measured by the percent of patients achieving good glycemic control (HbA_{1c} < 6.5% or HbA_{1c} < 7%) the efficacy of PIO 15 mg was approximately the same as MUR 1.5 mg

Glycemic Response at Week 24 - HbA_{1c} (LOCF)

| | 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 | 216 | 235 | 227 | 231 | 227 | 230 |
| HbA _{1c} ≤ 6.5% n (%) | 39 (18) | 68 (29) | 97 (43) | 136 (59) | 157 (69) | 60 (26) |
| HbA _{1c} ≤ 7.0% n (%) | 70 (32) | 103 (44) | 141 (62) | 176 (76) | 193 (85) | 108 (47) |

Dataset: Randomized Subjects

Changes in lipids at 12 weeks are shown in the following table:

| Lipid Parameter | n | BMS-298585 | | | | | pioglitazone ^a |
|---|----------|--------------------|--------------------|-------------------|--------------------|--------------------|---------------------------|
| | | 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) | n | 230 | 251 | 234 | 244 | 236 | 243 |
| Baseline Mean (SD) | | 201.04 (155.65) | 188.73 (136.17) | 186.30 (116.0) | 194.52 (240.96) | 176.22 (107.27) | 189.14 (114.15) |
| Adjusted Mean % Change from Baseline (SE) | | -3.74 (2.32) | -6.47 (2.16) | -21.10 (1.89) | -31.71 (1.60) | -40.96 (1.41) | -9.25 (2.11) |
| 95% CI relative to BMS-298585 0.5 mg | | -- | (-9.00, 3.74) | (-23.31, -12.38) | (-33.59, -24.22) | (-42.61, -34.45) | NA |
| HDL-C (mg/dL) | n | 230 | 252 | 234 | 244 | 236 | 244 |
| Baseline Mean (SD) | | 43.09 (10.13) | 43.44 (10.14) | 42.37 (9.64) | 43.15 (10.46) | 43.36 (10.02) | 43.14 (10.27) |
| Adjusted Mean % Change from Baseline (SE) | | 5.87 (1.06) | 7.84 (1.03) | 17.37 (1.16) | 19.85 (1.16) | 22.77 (1.21) | 10.01 (1.04) |
| 95% CI relative to BMS-298585 0.5 mg | | -- | (-0.87, 4.66) | (7.84, 13.97) | (10.15, 16.34) | (12.81, 19.20) | NA |
| LDL-C (mg/dL) | n | 230 | 251 | 234 | 244 | 236 | 242 |
| Baseline Mean (SD) | | 123.70 (35.19) | 122.76 (31.94) | 121.66 (33.52) | 125.73 (35.14) | 123.49 (33.16) | 127.13 (37.33) |
| Adjusted Mean % Change from Baseline (SE) | | 3.29 (1.41) | -1.67 (1.29) | 2.98 (1.40) | -0.06 (1.33) | -7.44 (1.25) | 3.18 (1.36) |
| 95% CI relative to BMS-298585 0.5 mg | | -- | (-8.27, -1.19) | (-4.00, 3.54) | (-6.80, 0.45) | (-13.71, -6.94) | NA |
| apoB (mg/dL) | n | 157 | 194 | 192 | 201 | 200 | 178 |
| Baseline Mean (SD) | | 108.93 (34.57) | 109.40 (49.02) | 106.22 (26.90) | 112.75 (41.33) | 107.52 (28.11) | 108.75 (25.07) |
| Adjusted Mean % Change from Baseline (SE) | | -2.59 (1.50) | -4.98 (1.32) | -9.65 (1.26) | -15.74 (1.15) | -22.05 (1.06) | -4.73 (1.35) |
| 95% CI relative to BMS-298585 0.5 mg | | -- | (-6.34, 1.59) | (-10.95, -3.40) | (-16.92, -9.94) | (-23.15, -16.69) | NA |

Demographic characteristics of patients who entered the long-term phase and their rescue status are shown in the following tables:

Demographic and Baseline Characteristics for Non-titrated Regimens

| Characteristic | Mur 1.5 mg N = 75 | Mur 5 mg N = 108 | Mur 10 mg N = 156 | Mur 20 mg N = 75 | Pio 15 mg N = 65 |
|--------------------------|----------------------|---------------------|----------------------|---------------------|---------------------|
| Age, years Mean (SD) | 56.0 (9.7) | 56.6 (8.5) | 55.4 (9.5) | 53.3 (9.4) | 54.1 (8.7) |
| Gender, n (%) | | | | | |
| Male | 41 (54.7) | 54 (50) | 81 (51.9) | 47 (62.7) | 38 (58.5) |
| Female | 34 (45.3) | 54 (50) | 75 (48.1) | 28 (37.3) | 27 (41.5) |
| Race, n (%) | | | | | |
| White | 65 (86.7) | 91 (84.3) | 129 (82.7) | 61 (81.3) | 58 (89.2) |
| Black | 4 (5.3) | 10 (9.3) | 9 (5.8) | 4 (5.3) | 1 (1.5) |
| Other | 6 (8.0) | 7 (6.5) | 18 (11.5) | 10 (13.3) | 6 (9.2) |
| BMI (kg/m ²) | | | | | |
| Mean (SD) | 30.8 (4.1) | 31.6 (4.6) | 31.0 (4.3) | 31.6 (4.5) | 32.8 (4.2) |
| HbA _{1c} (%) | | | | | |
| Mean (SD) | 7.6 (0.8) | 7.8 (0.8) | 8.0 (0.9) | 8.1 (1.1) | 7.5 (0.8) |

Dataset: Randomized Subjects who Started LT

N = number of subjects in regimen

Rescue/Titration Status of Randomized Subjects who Started the Long-term Phase

| Status | Randomized Treatment Groups | | | | | |
|-------------------------------|-----------------------------|---------------|-------------|--------------|---------------------------|--------------|
| | Mur 0.5 mg ^a | Mur 1.5 mg | Mur 5 mg | Mur 10 mg | Mur 20 mg ^b | Pio 15 mg |
| Total number of subjects | 136 | 166 | 182 | 191 | 164 | 146 |
| Never rescued/titrated, n (%) | 0 | 75 (45.2) | 108 (59.3) | 156 (81.7) | 75 (45.7) | 65 (44.5) |
| Rescued/titrated, n (%) | 136 (100) | 91 (54.8) | 74 (40.7) | 35 (18.3) | 89 (54.3) | 81 (55.5) |

^a All subjects in the Mur 0.5 group were titrated to Mur 1.5 mg at the start of long-term phase per -----

b) per protocol, patients on 20 mg Mur were entered into the long-term phase on 10 mg.

During the long-term extension phase, patients on submaximal therapy (less than MUR 10 mg or PIO 45) were titrated to the next highest dose of study drug based on the following glycemic criteria:

In the Period C long-term extension phase, all doses of study medication (other than muraglitazar 10 mg and pioglitazone 45 mg) may have been titrated to the next available dose every 6-12 weeks based upon a lack of glycemic control (MDG > 180 mg/dL for Weeks 30 and 36; HbA_{1c} > 8.0% for Weeks 48, 60, and 72; HbA_{1c} > 7.5% for Weeks 84 and 96; HbA_{1c} > 7.0% for Weeks 108 and 120). For subjects who reached the maximum allowable dose for their treatment regimen (muraglitazar 10 mg or pioglitazone 45 mg) and needed additional glycemic control, the investigator may have added adjunctive oral antihyperglycemic medication to a subject's long-term treatment regimen. The need for adjunctive medication was determined by the IVRS based upon the prespecified glycemic parameters described in the protocol.

An optional, 2-year double-blind extension of the protocol is currently ongoing.

The primary efficacy outcome for Period C was the change in HbA1c from baseline to 104 weeks, LOCF. This result is shown in the following table for patients who completed the short term study and stayed on their original dose during the long-term study.

Hemoglobin A_{1c} Change from Baseline to Week 104 (LOCF) for Non-titrated Regimens

| HbA _{1c} (%) | Mur 1.5 mg N = 75 | Mur 5 mg N = 108 | Mur 10 mg N = 156 | Mur 20 mg N = 75 | Pio 15 mg N = 65 |
|--------------------------------|----------------------|---------------------|----------------------|---------------------|---------------------|
| n | 75 | 108 | 156 | 75 | 65 |
| Baseline Mean (SD) | 7.58 (0.85) | 7.81 (0.83) | 7.97 (0.94) | 8.14 (1.06) | 7.53 (0.77) |
| Mean Change from Baseline (SE) | -0.92 (0.12) | -1.55 (0.09) | -1.78 (0.08) | -1.93 (0.14) | -1.07 (0.10) |
| 95% CI | (-1.15, -0.68) | (-1.74, -1.37) | (-1.93, -1.62) | (-2.21, -1.65) | (-1.28, -0.86) |

Dataset: Randomized Subjects who started LT

N = number of subjects in regimen; n = number of subjects in regimen with both a baseline and a post-baseline value

Change from baseline = Week 104 (LOCF) value - baseline value

The following table shows change from baseline, as analyzed by maximal achieved dose. The mean reduction in HbA1c at 104 weeks of MUR 5 mg was 1.34% and final HbA1c was 6.51%. The mean reduction in HbA1c at 104 weeks for PIO 45 mg was 0.97% and final HbA1c was 7.47%.

Table LTI 10.1.1A: Change from Baseline in HbA1c at Week 104 (LOCF) by Maximum Dose During Short-Term Combined with Long-Term Phase

| Regimen (mg) | N | HbA _{1c} (%) | | | | | | |
|--------------|-----|-----------------------|------|----------|------|----------------------|------|----------------|
| | | Baseline | | On-Study | | Change from Baseline | | |
| | | Mean | SD | Mean | SD | Mean | SE | (95% CI) |
| Mur Max 1.5 | 120 | 7.56 | 0.81 | 6.65 | 1.15 | -0.91 | 0.11 | (-1.12, -0.68) |
| Mur Max 5 | 184 | 7.85 | 0.79 | 6.51 | 0.74 | -1.34 | 0.08 | (-1.50, -1.18) |
| Mur Max 10 | 235 | 8.08 | 0.92 | 6.52 | 0.83 | -1.57 | 0.07 | (-1.71, -1.43) |
| Mur Max 20 | 231 | 8.20 | 1.02 | 6.53 | 1.17 | -1.66 | 0.08 | (-1.82, -1.50) |
| Pio Max 15 | 64 | 7.52 | 0.77 | 6.45 | 0.55 | -1.07 | 0.11 | (-1.28, -0.86) |
| Pio Max 45 | 68 | 8.44 | 0.87 | 7.47 | 1.00 | -0.97 | 0.17 | (-1.30, -0.64) |

Source: Appendix LTI 10.1.1A

Dataset: Randomized Subjects who started LT

N = Number of subjects in regimen with both a baseline and a post-baseline value

Change from baseline = Week 104 value - baseline value

(NOTE: In table shown above, patients randomized to 20 mg during the short term phase received 10 mg per day during the long term phase.)

Changes in lipids are shown in the following table. A dose-dependent fall in triglyceride and rise in HDL are noted.

Muraglitazar
BMS-298585

CV168006 LTI
Interim Study Report

Table LTI 10.3.1.1A: Percent Change from Baseline (Geometric Mean) in Lipids at Week 104 in the Short-term Combined with Long-term Phase for Non-titrated Regimens

| Parameter | Mur 1.5 mg N=75 | Mur 5 mg N=108 | Mur 10 mg N=156 | Mur 20 mg N=75 | Pio 15 mg N=65 |
|--|--------------------|-------------------|--------------------|-------------------|-------------------|
| TG (mg/dL), n | 46 | 73 | 114 | 14 | 43 |
| Baseline Geometric Mean (SE) | 136.20 (10.32) | 156.37 (8.49) | 155.16 (8.15) | 138.40 (13.71) | 145.02 (9.82) |
| Geometric Mean Percent Change from Baseline (SE) | -13.19 (6.05) | -22.40 (4.02) | -30.80 (2.99) | -38.68 (4.19) | -12.32 (5.12) |
| 95% CI | (-24.56, -0.10) | (-30.01, -13.96) | (-36.49, -24.62) | (-47.11, -28.92) | (-22.07, -1.36) |
| HDL-C (mg/dL), n | 47 | 73 | 114 | 14 | 45 |
| Baseline Geometric Mean (SE) | 42.51 (1.42) | 39.78 (0.99) | 40.21 (0.82) | 41.50 (1.59) | 41.67 (1.33) |
| Geometric Mean Percent Change from Baseline (SE) | 17.24 (2.93) | 28.89 (2.65) | 25.49 (2.25) | 27.68 (4.65) | 17.71 (2.64) |
| 95% CI | (11.50, 23.28) | (23.72, 34.27) | (21.11, 30.02) | (18.03, 38.13) | (12.50, 23.15) |
| LDL-C (mg/dL), n | 46 | 73 | 114 | 14 | 42 |
| Baseline Geometric Mean (SE) | 117.94 (5.36) | 116.72 (4.06) | 123.11 (3.29) | 126.31 (9.59) | 122.87 (5.97) |
| Geometric Mean Percent Change from Baseline (SE) | -9.83 (3.98) | -5.81 (3.37) | -5.31 (2.93) | -6.52 (3.50) | -8.05 (3.82) |
| 95% CI | (-17.49, -1.45) | (-12.29, 1.15) | (-10.94, 0.67) | (-13.78, 1.36) | (-15.44, 0) |
| TC (mg/dL), n | 47 | 73 | 114 | 14 | 45 |
| Baseline Geometric Mean (SE) | 193.39 (5.79) | 193.10 (4.34) | 199.81 (3.91) | 198.31 (10.74) | 195.36 (6.03) |
| Geometric Mean Percent Change from Baseline (SE) | -3.82 (3.04) | -1.06 (2.44) | -2.80 (1.98) | -3.80 (2.69) | -1.77 (2.73) |
| 95% CI | (-9.74, 2.49) | (-5.80, 3.93) | (-6.66, 1.21) | (-9.44, 2.18) | (-7.12, 3.89) |

161

Change in body weight:

At Week 104, baseline mean weight ranged from 87.95 kg to 94.10 kg for all non-titrated regimens. At Week 104, there was a mean increase from baseline for all dose groups: 0.56 kg for the muraglitazar 1.5 mg group, 5.86 kg for the muraglitazar 5 mg group, 8.94 kg for the muraglitazar 10 mg group, 9.01 kg for the muraglitazar 20 mg group and 1.91 kg for the pioglitazone 15 mg non-titrated regimen. There was also a mean increase from baseline in body weight at Week 104 by maximum dose: 0.69 kg for the muraglitazar 1.5 mg group, 5.18 kg for the muraglitazar 5 mg group, 8.59 kg for the muraglitazar 10 mg group, and 8.88 kg for the muraglitazar 20 mg maximum group, 1.80 kg for the pioglitazone 15 mg group and 4.68 kg for the pioglitazone 45 mg maximum group.

Combination Therapy

Three 24-week, randomized, double-blind, controlled, combination studies evaluated the effects of MURAGLITAZAR on glycemic control in patients with type 2 diabetes who were inadequately controlled with metformin or sulfonylurea. Patients had HbA1c of 7-10% at baseline and were withdrawn during the blinded treatment for poor glycemic control based on FPG as follows: week 6 >240 mg/dl, week 8 > 220 mg/dl, weeks 12, 16, and week 20 > 200 mg/dl

Combination Therapy with Metformin

Trial 022 - Placebo-Controlled Combination Therapy with Metformin

This was a placebo controlled trial in patients with type 2 diabetes on existing metformin therapy (1500-2500g/dl, approximate average daily dose: 1850 mg) for at least six weeks with HbA1c at screening between 7 and 10%. Patients were randomized to the addition of either MURAGLITAZAR 2.5 mg or 5 mg, or placebo once daily. At baseline, patients on MUR or placebo had a mean BMI of 31.3 and mean HbA1c of 8.0%. A slight imbalance with respect to gender, race and age between MUR and placebo patients is noted in the following table:

Demographic and Baseline Characteristics

| Characteristic | MUR 2.5 + MET N = 233 | MUR 5 + MET N = 205 | PLA + MET N = 214 |
|-----------------------|----------------------------------|--------------------------------|------------------------------|
| Age, years | | | |
| Mean (SD) | 54.9 (8.1) | 54.1 (9.2) | 55.9 (8.3) |
| Gender, n (%) | | | |
| Male | 132 (56.7) | 116 (56.6) | 111 (51.9) |
| Female | 101 (43.3) | 89 (43.4) | 103 (48.1) |
| Race, n (%) | | | |
| White | 205 (88.0) | 180 (87.8) | 195 (91.1) |
| Black | 16 (6.9) | 13 (6.3) | 9 (4.2) |
| Other | 12 (5.2) | 12 (5.9) | 10 (4.7) |

Change in the primary variable, HbA1c, is shown in the following table:

| Primary Efficacy Endpoint: Hemoglobin A_{1c} Change from Baseline at Week 24 (LOCF) | | | |
|--|----------------------------------|--------------------------------|------------------------------|
| HbA_{1c} Measurement (%) | MUR 2.5 + MET N = 233 | MUR 5 + MET N = 205 | PLA + MET N = 214 |
| n | 222 | 198 | 197 |
| Baseline Mean (SD) | 7.99 (0.99) | 8.00 (0.99) | 7.97 (1.01) |
| Adjusted Mean Change from Baseline (SE) | -0.91 (0.06) | -1.16 (0.07) | -0.05 (0.07) |
| Difference in Adjusted Mean Change from Baseline (SE) vs PLA + MET ^a | -0.86 (0.09) | -1.11 (0.10) | |
| 95% 2-sided CI | (-1.04, -0.67) | (-1.30, -0.92) | |
| p-value ^b | <.0001 ^c | <.0001 ^c | |

Dataset: Randomized Subjects

Note: ANCOVA model: post-pre=pre treatment.

^a Estimate = Adjusted mean change - adjusted mean change for PLA + MET

^b p-value is obtained using non-parametric method.

^c Statistically significant at $\alpha = 0.05$ using Koch-Ganskv sequential testing procedure.

Compared to placebo, the addition of MURAGLITAZAR showed a clinically significant improvement in glycemic control as measured by A1C and FPG as well as a reduction in FFA (see **Table**).

| Glycemic and Related Parameters in Placebo-Controlled Combination Study with Metformin at Week 24 | | | |
|--|--------------------------------|---------------------------------|-------------|
| | Placebo + Metformin | MURAGLITAZAR + Metformin | |
| | | 2.5 mg | 5 mg |
| | N=197 | N=222 | N=198 |
| A1C (%) | | | |
| Baseline (mean) | 8.0 | 8.0 | 8.0 |
| Mean change from baseline | 0.0 | -0.9* | -1.2* |
| % patients with final A1C <7% | 27% | 54% | 64% |
| FPG (mg/dL) | | | |
| Baseline (mean) | 171 | 169 | 167 |
| Mean change from baseline | -2 | -26* | -35* |
| Free Fatty Acids (mEq/L) | | | |
| Baseline (mean) | 0.7 | 0.7 | 0.7 |
| Mean % change from baseline | -7% | -18% | -28% |

*p<0.0001 vs. placebo

At Week 12, MURAGLITAZAR 2.5 mg and 5 mg produced greater decreases in TG and greater increases in HDL-C compared to placebo.

| Lipid Parameters in Placebo-Controlled Combination Study with Metformin at Week 12 | | | |
|---|----------------------------|---------------------------------|-------------|
| | Placebo + Metformin | MURAGLITAZAR + Metformin | |
| | | 2.5 mg | 5 mg |
| | N=212 | N=228 | N=201 |
| Triglycerides (mg/dL) | | | |
| Baseline (mean) | 197 | 198 | 208 |
| Mean % change from baseline | 3% | -14%* | -29%* |
| HDL-C (mg/dL) | | | |
| Baseline (mean) | 46 | 45 | 46 |
| Mean % change from baseline | 1% | 8%** | 14%** |
| apoB (mg/dL) | | | |
| Baseline (mean) | 99 | 100 | 100 |
| Mean % change from baseline | 1% | -5% | -12% |
| LDL-C (mg/dL) | | | |
| Baseline (mean) | 106 | 107 | 106 |
| Mean % change from baseline | 5% | 9% | 5% |
| non-HDL-C (mg/dL) | | | |
| Baseline (mean) | 143 | 145 | 146 |
| Mean % change from baseline | 4% | 2% | -5% |

* p<0.0001 vs. placebo

**nominal p-value <0.0001 vs. placebo

The mean body weight in the three groups was about 89 kg at baseline. The adjusted mean at 24 weeks, LOCF was 1.40 and 2.76 kg for MUR 2.5 mg and 5 mg, respectively and -0.73 kg for placebo.

Trial 025: Active-Controlled (MUR vs PIO) Study of Combination Therapy with Metformin

In this double-blind, metformin combination study, 1159 patients with type 2 diabetes on existing metformin therapy were randomized to the addition of either MURAGLITAZAR 5 mg or pioglitazone 30 mg once daily for 24 weeks. At screening, patients had HbA1c 7-10% while on a stable dose of metformin (1500 mg to 2550 mg, approximate average daily dose = 1850 mg) for at least six weeks. Patients continued metformin open label and were randomized to either MUR 5-mg tablets plus placebo-matching PIO capsule, or PIO 30-mg capsule, plus placebo-matching MUR tablet. The primary analysis was change in HbA1c at 24 weeks, LOCF. The study was constructed to show non-inferiority of MUR vs PIO with a margin of 0.25 % units (upper limit of the 95% CI for difference in change in HbA1c). If non-inferiority was met further testing of superiority was described.

Baseline characteristics are shown in the following table:

Demographics and Baseline Disease Characteristics

| Characteristic | Muraglitazar 5 mg plus Metformin N=587 | Pioglitazone 30 mg plus Metformin N=572 |
|------------------------|--|---|
| Age, years | | |
| Mean (SD) | 55.3 (8.6) | 54.1 (9.1) |
| Gender, n (%) | | |
| Male | 269 (45.8) | 280 (49.0) |
| Female | 318 (54.2) | 292 (51.0) |
| Race, n (%) | | |
| White | 526 (89.6) | 514 (89.9) |
| Black | 49 (8.3) | 40 (7.0) |
| Other | 12 (2.0) | 18 (3.1) |
| BMI, kg/m ² | | |
| Mean (SD) | 32.0 (4.6) | 32.0 (4.6) |
| HbA _{1c} , % | | |
| Mean ^a (SD) | 8.1 (1.0) | 8.1 (1.0) |

Dataset: Randomized Subjects

Note N = Number of randomized subjects; n = Number of randomized subjects with available data.

Note: BMI is calculated by weight (kg)/[height(m)²].

^a N = 586 for HbA_{1c} in the muraglitazar 5 mg plus metformin group, as Subject CV168025-131-5 had no baseline value.

Change in the primary variable, HbA1c is shown in the following table:

Primary Efficacy Endpoint: HbA_{1c} Change from Baseline at Week 24 LOCF

| HbA _{1c} Measurement (%) | Muraglitazar 5mg plus Metformin N=587 | Pioglitazone 30 mg plus Metformin N=572 |
|--|--|--|
| n | 569 | 550 |
| Baseline Mean (SD) | 8.12 (0.96) | 8.13 (1.00) |
| Adjusted Mean Change from Baseline (SE) | -1.14 (0.04) | -0.85 (0.04) |
| Difference in Adjusted Mean Change from Baseline | | |
| Mean (SE) | -0.29 (0.05) | |
| 95% 2-sided CI | (-0.39, -0.19) | |
| p-value ^a | < 0.0001 ^b | |

Dataset: Randomized Subjects

Note ANCOVA model: post-pre=pre treatment.

^a p-value obtained using non-parametric method.

^b Statistically significant at $\alpha = 0.05$ after having demonstrated the non-inferiority of muraglitazar 5 mg plus metformin versus pioglitazone 30 mg plus metformin.

As shown below MURAGLITAZAR produced greater reductions in A1C, FPG, and FFA than Pioglitazone.

| Glycemic and Related Parameters in Active-Controlled Combination Study with Metformin at Week 24 | | |
|---|---------------------------------|---------------------------------|
| | MURAGLITAZAR + Metformin | Pioglitazone + Metformin |
| | 5 mg | 30 mg |
| | N=569 | N=550 |
| A1C (%) | | |
| Baseline (mean) | 8.1 | 8.1 |
| Mean change from baseline | -1.1 | -0.8 |
| Between treatment difference | -0.3* | |
| % patients with final A1C <7% | 60% | 44% |
| FPG (mg/dL) | | |
| Baseline (mean) | 179 | 178 |
| Mean change from baseline | -44 | -33 |
| Free Fatty Acids (mEq/L) | | |
| Baseline (mean) | 0.7 | 0.7 |
| Mean % change from baseline | -24% | -15% |

*p<0.0001 vs. pioglitazone

At Week 12, MURAGLITAZAR produced greater decreases in TG and apoB, and greater increases in HDL-C compared to pioglitazone.

| Percent Change from Baseline in TG, HDL-C, apoB, and non-HDL-C at Week 11/12 LOCF | | |
|--|--|--|
| Lipid Parameter | Muraglitazar 5mg plus Metformin N=587 | Pioglitazone 30 mg plus Metformin N=572 |
| TG (mg/dL), n | 571 | 555 |
| Baseline Mean (SD) | 205.50 (125.09) | 202.75 (128.44) |
| Adjusted Mean % Change from BL (SE) | -28.43 (0.89) | -14.44 (1.08) |
| 95% 2-sided CI | (-19.22, -13.39) | |
| Rank p-value | <0.0001 | |
| HDL-C (mg/dL), n | 571 | 555 |
| Baseline Mean (SD) | 46.29 (11.12) | 45.92 (11.14) |
| Adjusted Mean % Change from BL (SE) | 19.16 (0.58) | 13.61 (0.56) |
| 95% 2-sided CI | (3.47, 6.32) | |
| Rank p-value | <0.0001 | |
| apoB (mg/dL), n | 571 | 555 |
| Baseline Mean (SD) | 100.85 (24.64) | 100.61 (26.78) |
| Adjusted Mean % Change from BL (SE) | -11.75 (0.62) | -5.96 (0.67) |
| 95% 2-sided CI | (-7.98, -4.29) | |
| Rank p-value | <0.0001 | |
| Non-HDL-C (mg/dL), n | 571 | 555 |
| Baseline Mean (SD) | 152.26 (39.67) | 150.71 (39.03) |
| Adjusted Mean % Change from BL (SE) | -5.88 (0.62) | -1.22 (0.66) |
| 95% 2-sided CI | (-6.46, -2.94) | |
| Rank p-value | <0.0001 | |

Dataset: Randomized Subjects

Weight:

The adjusted mean change from baseline at Week 24 LOCF in body weight was moderately higher for the muraglitazar 5 mg plus metformin group (1.39 kg) relative to the pioglitazone 30 mg plus metformin group (0.56 kg).

Trial 021 - Placebo-Controlled Combination Therapy with Glyburide

This was a placebo-controlled trial in patients with type 2 diabetes on sulfonylurea therapy. Eligible patients were taking 10-20 mg/d of Glyburide, or at least 50% maximal labeled dose of sulfonylurea other than glyburide for at least six weeks before screening, or 20 mg of glyburide for at least two weeks before screening. Subjects were required to have the following laboratory findings at screening: HbA1c between 7 and 10%, Triglyceride less than or equal to 600 mg/dl, fasting C-peptide at least 1.5 ng/dl, BMI less than or equal to 41 kg/m². After screening, there was a two-week, diet/exercise, placebo run-in during which time all patients received 15 mg Glyburide. Compliance was assessed by pill count. No down-titration of 15-mg glyburide was permitted. After the run-in, patients were randomized to the addition of either MURAGLITAZAR 2.5 mg or 5 mg, or placebo once daily in addition to 15 mg Glyburide. The blinded comparison lasted for 24 weeks, during which time down-titration of glyburide was permitted to prevent hypoglycemia (Down titration occurred in two patients on 2.5 mg MUR and one patients on 5 mg MUR who reported hypoglycemia as an SAE).

Baseline characteristics are shown in the following table:

| Demographic and Baseline Characteristics | | | |
|---|----------------------------------|--------------------------------|------------------------------|
| Characteristic | MUR 2.5 + GLY N = 191 | MUR 5 + GLY N = 193 | PLA + GLY N = 199 |
| Age, years | | | |
| Mean (SD) | 54.8 (9.2) | 55.8 (8.8) | 54.7 (9.3) |
| Gender, n (%) | | | |
| Male | 104 (54.5) | 103 (53.4) | 109 (54.8) |
| Female | 87 (45.5) | 90 (46.6) | 90 (45.2) |
| Race, n (%) | | | |
| White | 158 (82.7) | 160 (82.9) | 169 (84.9) |
| Black | 14 (7.3) | 18 (9.3) | 18 (9.0) |
| Other | 19 (9.9) | 15 (7.8) | 12 (6.0) |
| BMI, kg/m ² | | | |
| Mean (SD) | 30.2 (4.9) | 30.3 (4.5) | 31.2 (5.1) |
| HbA _{1c} , % | | | |
| Mean (SD) | 7.9 (1.1) | 8.2 (1.1) | 8.2 (1.0) |

Dataset: Randomized Subjects

Note: N = Number of Randomized Subjects; n = Number of Randomized Subjects with available data

Note: BMI is calculated by weight (kg)/[height(m)*height(m)]. MUR = muraglitazar; GLY = glyburide; PLA = placebo.

As shown in the following table, both doses of MUR were better than placebo with respect to change in the primary variable, HbA1c

| Primary Efficacy Endpoint: Hemoglobin A_{1c} Change from Baseline at Week 24 (LOCF) | | | |
|--|----------------------------------|--------------------------------|------------------------------|
| HbA_{1c} Measurement (%) | MUR 2.5 + GLY N = 191 | MUR 5 + GLY N = 193 | PLA + GLY N = 199 |
| n | 176 | 189 | 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 in Adjusted Mean Change from Baseline (SE) vs PLA + GLY ^a | -1.15 (0.10) | -1.37 (0.10) | |
| 95% 2-sided CI | (-1.35, -0.96) | (-1.55, -1.18) | |
| p-value ^b | <.0001 ^c | <.0001 ^c | |

Dataset: Randomized Subjects

Note: ANCOVA model: post-pre = pre treatment.

^a Estimate = Adjusted mean change - adjusted mean change for PLA + GLY

^b p-value is obtained using non-parametric method.

^c Statistically significant at $\alpha = 0.05$ using Koch-Gansky sequential testing procedure.

MUR was also better than placebo with respect to reduction in FPG and Free fatty acids.

| Glycemic and Related Parameters in Placebo-Controlled Combination Study with Sulfonylurea at Week 24 | | | |
|---|-------------------------------|------------------------------------|-------------|
| | Placebo + Sulfonylurea | MURAGLITAZAR + Sulfonylurea | |
| | | 2.5 mg | 5 mg |
| | N=195 | N=176 | N=189 |
| A1C (%) | | | |
| Baseline (mean) | 8.2 | 7.9 | 8.2 |
| Mean change from baseline | 0.2 | -1.0* | -1.2* |
| % patients with final A1C <7% | 13% | 52% | 59% |
| FPG (mg/dL) | | | |
| Baseline (mean) | 167 | 162 | 169 |
| Mean change from baseline | 12 | -27* | -36* |
| Free Fatty Acids (mEq/L) | | | |
| Baseline (mean) | 0.6 | 0.6 | 0.7 |
| Mean % change from baseline | -3% | -17% | -21% |

*p<0.0001 vs. placebo

Weight

The adjusted mean change from baseline at Week 24 LOCF in body weight was 2.63 kg and 4.06 kg in the muraglitazar 2.5 mg or 5 mg plus glyburide groups, respectively, relative to 0.43 kg in the placebo plus glyburide group.

At Week 12, MURAGLITAZAR 2.5 mg and 5 mg produced greater decreases in TG and greater increases in HDL-C than placebo.

| Lipid Parameters in Placebo-Controlled Combination Study with Sulfonylurea at Week 12 | | | |
|--|-------------------------------|------------------------------------|-------------|
| | Placebo + Sulfonylurea | MURAGLITAZAR + Sulfonylurea | |
| | | 2.5 mg | 5 mg |
| | N=197 | N=183 | N=192 |
| Triglycerides (mg/dL) | | | |
| Baseline (mean) | 193 | 197 | 204 |
| Mean % change from baseline | 3% | -14%* | -26%* |
| HDL-C (mg/dL) | | | |
| Baseline (mean) | 44 | 44 | 44 |
| Mean % change from baseline | 0% | 7%** | 14%** |
| apoB (mg/dL) | | | |
| Baseline (mean) | 103 | 104 | 107 |
| Mean % change from baseline | 0% | -5% | -11% |
| LDL-C (mg/dL) | | | |
| Baseline (mean) | 118 | 119 | 121 |
| Mean % change from baseline | 3% | 4% | 2% |
| non-HDL-C (mg/dL) | | | |
| Baseline (mean) | 156 | 156 | 161 |
| Mean % change from baseline | 2% | -1% | -6% |

* p<0.0001 vs. placebo

**nominal p-value <0.0001 vs. placebo

6.1.5 NA

6.1.6 Efficacy Conclusion

The five trials in this review establish the efficacy of Muraglitazar with respect to reduction in HbA1c. The response was durable up to 108 weeks. In addition to reducing HbA1c, Muraglitazar reduced blood triglyceride levels and increased HDL. Its activity is similar to Pioglitazone except that Muraglitazar appears to be about 10x more potent than Pioglitazone. 1.5 mg of MUR was found to have the same activity as 15 mg of pioglitazone. 5 mg of MUR was found to have more activity than 30 mg of pioglitazone.

The Sponsor proposes to market MUR in 2.5 and 5-mg strengths. Consideration should also be given to marketing the 1.5-mg strength as well. This strength also gives results that are statistically and clinically significant. For instance, in trial 006, 1.5 mg of MUR gave a reduction in HbA1c of 0.92% units (baseline 7.58%) at 104 weeks, which associated with a 13% fall in triglyceride (baseline 136 mg/dl) and 17% rise in HDL (baseline 43 mg/dl).

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

/s/

Robert Misbin
8/5/05 09:03:25 AM
MEDICAL OFFICER

David Orloff
8/5/05 12:26:40 PM
MEDICAL OFFICER