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GENERIC DRUG NAME / COMPOUND NUMBER: PPM-204 / WAY-283204

PROTOCOL NO.: 3180A1-103-WW

PROTOCOL TITLE: A 4-Week Randomized, Parallel, Double-Blind, Placebo-Controlled Multicenter Study of the Preliminary Efficacy, Safety, and Pharmacokinetics of PPM-204 Administered Orally to Treatment-Naïve Subjects With Type 2 Diabetes Mellitus

Study Centers: Seven (7) centers took part in the study and enrolled subjects; 4 centers in Russia, and 1 center each in Denmark, Germany and the United States (US).

Study Initiation and Final Completion Dates: April 2006 to 08 February 2007

Phase of Development: Phase 2A

Study Objectives:

Primary Objective: To determine the glucose lowering effects of PPM-204 in subjects diagnosed with type 2 diabetes mellitus (T2DM).

Secondary Objective: To assess the safety and pharmacokinetics (PK) of multiple oral doses of PPM-204 in subjects with T2DM.

METHODS

Study Design: This was a randomized, parallel, double-blind, placebo-controlled, and active-controlled study of 4 doses of PPM-204 administered orally once daily for 28 days to subjects with T2DM. Subjects were assigned to randomly receive 1 of 4 doses of PPM-204, 30-mg of pioglitazone, or placebo. The study was initially planned to assess only 3 doses of PPM-204 (25, 75, and 225 mg). From 01 May 2006 an additional dose of PPM-204 (450-mg) was approved for use in the US only. The remaining sites continued to follow the initial plan, thereby using only 3 doses of PPM-204. As a result, at the time the study was completed only 2 subjects were randomly assigned to receive PPM-204 at a dose of 450 mg/day. All data from these 2 subjects is provided; however, because of the small size of the 450 mg/day group, data from this group was not included in the statistical analyses for the various cohorts or in the comparisons among the PPM-204, pioglitazone, or the placebo groups.

Each subject participated in the study for approximately 9 weeks. Participation included a screening evaluation within 3 weeks before test article administration, a 28-day active treatment period, and an end-of-study follow-up period 2 weeks after study discharge. It was

estimated that the clinical portion of the study would be completed in approximately 6 months. Table 1 presents the schedule of activities for this study.

Table 1. Schedule of Activities

Study Phase	Screening		Treatment Period		Final Study Evaluation	Follow-Up
Study Day	**-21 to -2**	**-1**	**1**	**2-27**	**28**	**42 (±2 days)**
Informed consent	X					
Outpatient visit	X	X	X	X[a]	X	X
Medical history	X					
Physical examination	X[b]	X		X[c]	X	X
Body weight (kg)	X	X	X	X[d]	X	X
Waist circumference (cm)		X		X[e]	X	
Edema assessment[f]		X	X	X[d]	X	X
Vital signs[g]	X	X	X	X[d]	X	X
ECG (12-Lead)	X	X		X[d]	X	X
Laboratory evaluation[h]	X	X	X	X[d]	X	X
Fasting insulin	X		X	X[d]		X
Fasting lipid profile	X	X			X	X
Thyroid stimulating hormone and free T4	X			X[e]	X	X
Troponin I and T, CPK MB, BNP	X			X[e]	X	X
C-peptide, HbA1C	X					
Adiponectin, IL-6, TNF-α, fructosamine		X			X	X
Vascular endothelial growth factor		X			X	X
Cystatin C		X		X[e]	X	
Oral glucose tolerance test[i]		X			X	
Urine PGE_2		X		X[e]	X	
Pregnancy test (women only)	X	X			X	X
HIV and HCV antibody screen	X					
Hepatitis B surface antigen screen	X					
Dispensing of test article			X[j]			
Test article administration[k]			X	X	X	
Dietary maintenance	X[l]					
PK and metabolite blood sample collection			X[m]	X[m]	X[n]	
Concomitant medication monitoring	X----------					----------X
Adverse events recording	X----------					----------X[o]

BNP = brain natriuretic peptide; CPK MB = creatinine phosphokinase muscle band; oxide; ECG = electrocardiogram; HbA1C = Hemoglobin A1C; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IL-6 = Interleukin-6; PGE_2 = prostaglandin E_2; PK = pharmacokinetic; T4 = thyroxine; TNF-α = tumor necrosis factor-α.

a. Subjects had outpatient visits on Study Days 7, 14, and 21. Visits occurred ±1 day.
b. Physical examination included height (cm) and weight (kg).
c. Brief physical assessment (performed by a registered nurse or physician's assistant) on Study Days 7, 14, and 21.
d. Measured on Study Days 7, 14, and 21.
e. Performed on Study Day 14 only.
f. Assessments included upper and lower extremities, sacral, and facial.
g. Sitting blood pressure, pulse rate, and respiratory rate after resting quietly for at least 5 minutes, and oral/tympanic temperature.
h. Hematology, fasting blood chemistry, and urinalysis.
i. Fasting glucose and insulin to be performed within 15 minutes prior to the oral glucose tolerance test, then at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, and 4 hours after the start of the test.
j. Dispensing of test article to subjects occurred on Day 1.
k. Subjects instructed to take oral test article (4 capsules) daily for 28 days in the morning at approximately the same time each day before breakfast except on all outpatient visit days. Subjects brought test article

Table 1. Schedule of Activities

with them at each outpatient visit, and took their daily dose at the clinical site.

l. Subjects maintained on a stable diet (American Diabetes Association or European Association for the Study of Diabetes) for 10 days before Study Day 1.

m. PK and metabolite samples taken on Study Days 1, 7, 14, and 21 within 2 hours before dose administration.

n. PK and metabolite sample taken within 2 hours before dose administration, and 1, 2, 4, and 6 hours after dose administration.

o. AE monitoring occurred from the time the subject signed the informed consent and until 15 days after the last dose of test article.

Number of Subjects (Planned and Analyzed): Approximately 108 subjects were planned to be enrolled to allow for the completion of at least 15 subjects in each of the initial 6 dose cohorts (total of 90 subjects). A total of 91 subjects were enrolled in the study (80 in Russia, 2 in Denmark, 1 in Germany and 8 in the US).

Diagnosis and Main Criteria for Inclusion and Exclusion: Men and women aged 30 to 80 years, inclusive, on Study Day 1; men who agreed to participate in this study understood that there was a risk when taking a drug whose effect on a fetus is unknown and must have used adequate barrier contraception (such as condoms) during the study period and for at least 60 days after study discharge; women of non-childbearing potential if they were either surgically sterile (hysterectomy and/or oophorectomy) or postmenopausal (defined as at least 12 months of spontaneous amenorrhea); diagnosed with T2DM at least 4 weeks before Study Day 1, subjects who had never received any pharmacologic treatment for diabetes with the sole exception of subjects who received a single short-term insulin treatment period, administered for no longer than 2 weeks and discontinued at least 3 months before Study Day 1, or subjects who had received oral hypoglycemic treatment for <1 month and that treatment ended at least 4 weeks before Study Day 1, or subjects who had received oral hypoglycemic treatment for >1 month but <1 year and that treatment ended at least 8 weeks before Study Day 1; subjects on a stable exercise regimen and a weight-maintenance diet as recommended by the American Diabetes Association or the European Association for the Study of Diabetes for at least 10 days before Study Day 1.

Exclusion Criteria: Subjects with history or current evidence of peripheral edema, venous insufficiency, peripheral vascular disease, clinically important neuropathy, stroke, active asthma within the last 5 years, drug abuse within 1 year before Study Day 1, non-steroidal anti-inflammatory drug induced bronchospasm, proliferative retinopathy, any blood or blood product transfusion within 90 days before Study Day 1, acute disease state (eg, nausea, vomiting, fever, diarrhea) within 7 days before Study Day 1.

Study Treatment: Subjects were instructed to take oral test article (4 capsules) daily for 28 days in the morning at approximately the same time each day before breakfast. Subjects were randomly assigned to 1 of the following treatment groups:

- PPM-204 25 mg (1 capsule 25 mg PPM-204; 2 placebo PPM-204; 1 placebo pioglitazone).

- PPM-204 75 mg (3 capsules 25 mg PPM-204; 0 placebo PPM-204; 1 placebo pioglitazone, or 1 capsule 75 mg PPM-204; 2 placebo PPM-204; 1 placebo pioglitazone).

- PPM-204 225 mg (3 capsules 75 mg PPM-204; 0 placebo PPM-204; 1 placebo pioglitazone) or (1 capsule 225 mg PPM-204; 2 placebo PPM-204; 1 placebo pioglitazone).

- PPM-204 450 mg (2 capsules 225 mg PPM-204; 1 placebo PPM-204; 1 placebo pioglitazone).

- Pioglitazone 30 mg (3 placebo PPM-204; 1 pioglitazone 30 mg).

- Placebo (3 placebo PPM-204; 1 placebo pioglitazone).

Pharmacodynamic and Pharmacokinetic Endpoints:

Pharmacodynamic Endpoints:

Primary Endpoints:

- Changes from Baseline of fasting plasma glucose (FPG), and of mean plasma glucose during oral glucose tolerance test (OGTT) on Day 28.

Secondary Endpoints:

- Fructosamine, fasting insulin, mean insulin during the OGTT, quantitative insulin-sensitivity check index (1/[log {fasting insulin} + log {fasting glucose}]), and insulin sensitivity index (10000/[square root of {fasting glucose × fasting insulin} × {mean glucose × mean insulin during OGTT}]).

- Lipid profile (total cholesterol, low-denisity lipoprotein [LDL], high-density lipoprotein [HDL], triglycerides, and free fatty acids).

- Adiponectin.

- Interleukin-6 and tumor necrosis factor-α.

Pharmacokinetic Endpoints:

- PPM-204 and conjugated metabolite concentrations on Study Days 1, 7, 14 and 21 within 2 hours before test article administration and on Study Day 28 within 2 hours before test article administration and 1, 2, 4 and 6 hours after test article administration.

No efficacy evaluations were performed for this study.

Safety Evaluations: Routine safety and tolerability was evaluated from the results of reported symptoms and signs, scheduled physical examinations, vital signs measurements, 12-lead electrocardiograms (ECGs), and clinical laboratory test results. In addition, brain

natriuretic peptide, troponin I and T, creatine phosphokinase muscle band, urine prostaglandin E, cystatin C, and vascular endothelial growth factor were evaluated.

Statistical Methods:

Per-Protocol Population: The per-protocol population included all subjects who had a pharmacodynamics evaluation at the time point being analyzed, whose test article compliance was >80%, as defined by the ratio of number of doses taken to that expected per-protocol, and who did not have a major study deviation.

Safety Population: The population for safety analysis included all subjects who received at least 1 dose of test article.

The majority of the statistical analysis was descriptive in nature. Limited hypothesis testing was performed, even though the p-values generated in this analysis were used to estimate strength of relationships rather than to determine efficacy definitively.

Analysis of PD effects was performed for the per-protocol population. For the primary PD endpoints, such as FPG and mean glucose during OGTT, statistical analysis of the mean change from Baseline to Week 4 was performed using a covariance model with terms for baseline measurement, treatment, and center. If the difference in number of subjects enrolled was large among centers, then the smaller centers may have been combined. Pairwise comparisons among treatment groups were performed for the identification of effective doses.

Using predetermined criteria, individual data for vital signs, ECGs, and laboratory test results were evaluated for potential clinical importance (PCI).

Demographic data and other baseline characteristics, which included age, sex, body mass index, FPG, Hemoglobin A1C, fasting insulin, and C-peptide were summarized by treatment using descriptive statistics to provide assessments of the performance of randomization.

RESULTS

Subject Disposition and Demography:

A total of 91 subjects were included in the study. Disposition and demography data is not available.

Pharmacodynamic Results:

Fasting Plasma Glucose: After 28 days of treatment, fasting glucose decreased significantly in the PPM-204 225 mg/day group and in the pioglitazone group (change from Baseline compared to placebo). No significant changes were observed in the PPM-204 25 or 75 mg/day groups on Day 28. Two (2) weeks after discontinuation of test article administration, on Study Day 42, the difference from placebo persisted for the PPM-204 225 mg/day group but not for the pioglitazone group. On Day 42 there was also a significant

difference in the PPM-204 75 mg/day group (in which there had been no significant difference on Day 28).

Fasting Insulin: Fasting insulin decreased significantly (change from Baseline compared to placebo) in the 225 mg/day group after 28 days of treatment but not in any of the other groups. On Day 42, the difference persisted for the PPM-204 225 mg/day group, and a significant difference was also noted for the PPM-204 75 mg/day group and for the pioglitazone group.

Glucose and Insulin: Mean change from Baseline in area under the concentration-time curve in 1 dosage interval (AUC_t) for glucose was -1.7, -10.4, and -36.4 mg/dL in the 25, 75, and 225 mg/day groups, respectively, 12.3 for placebo, and -11.8 for pioglitazone. Mean change from Baseline in AUC_t for insulin was -47.0, -30.1, and -59.9 p mol/L in the 25, 75, and 225 mg/day groups, respectively, -6.5 for placebo, and -10.4 for pioglitazone. In the PPM-204 225 mg/day group, the decrease in AUC_t that was noted for both glucose and insulin was significant compared to placebo. No significant change from placebo existed in any of the other treatment groups.

Adiponectin and Lipids: Adiponectin appeared to increase in a dose-dependent manner in the PPM-204 groups. Total cholesterol and LDL-cholesterol did not change significantly in any of the PPM-204 treatment groups over the 28 days of treatment. HDL-cholesterol increased in the PPM-204 225 mg/day group (difference from placebo in change from Baseline) by approximately 0.13 (11.7%) mmol/L, which was significant compared with that in the placebo group as well as to that in the pioglitazone group. The difference from placebo remained significant on Day 42, 2 weeks after discontinuation of test article. No significant changes were found in any of the other treatment groups, but there appeared to be a dose-dependent trend of an increase in HDL-cholesterol with increasing PPM-204 dose. Triglycerides were significantly decreased in the PPM-204 225 mg/day group as early as Day 14 compared with placebo and on Days 21 and 28 were significantly lower compared with both placebo and pioglitazone. On Day 42, 2 weeks after discontinuation of test article administration, triglycerides were not significantly different in the PPM-204 225 mg/day group from the placebo or pioglitazone groups.

No efficacy evaluations were performed for this study.

Safety Results: A total of 17 (18.7%) of 91 subjects experienced treatment-emergent adverse events (TEAEs) during the study; 11 (19.6%) of those subjects received PPM-204, 2 (11.8%) received pioglitazone, and 4 (22.2%) received placebo. Of the 11 (19.6%) subjects who received PPM-204 and experienced a TEAE, 1 (5.6%) received the 25 mg dose, 5 (27.8%) received the 75 mg dose, 4 (22.2%) received the 225 mg dose, and 1 (50%) received the 450-mg dose.

The most common TEAE was blood creatinine phosphokinase increased, reported for 2 (11.1%) subjects who received placebo and 2 (11.1%) subjects who received PPM-204 (1 subject on the 75 mg dose and 1 subject on the 225 mg dose). The number of TEAEs did not increase with increasing PPM-204 doses.

There were no deaths, other serious adverse events (SAEs), safety-related discontinuations, or other clinically important adverse events (AEs) during this study. The Medical Monitor reviewed the records of the subjects with PCI changes in laboratory test results, vital signs, and ECG findings, and determined that none of the changes were of clinical importance.

CONCLUSIONS: Fasting glucose and insulin decreased after 28 days of treatment with PPM-204 at a dose of 225 mg/day. Glucose and insulin after OGTT appeared to decrease in a dose-dependent manner. Adiponectin increased in a dose-dependent manner. HDL appeared to increase and triglycerides appeared to decrease in a dose-dependent manner. Multiple PPM-204 doses of up to 450 mg/day given for up to 28 days appeared safe and well tolerated in treatment-naïve subjects with T2DM. The number of TEAEs did not increase with increasing PPM-204 doses. There were no deaths, SAEs, safety-related discontinuations, or other clinically important AEs during this study. There were no clinically important changes in vital signs, ECG results, or physical findings. The peak concentrations and partial area under the curve determined using the 6-hour concentration-time profile values for PPM-204 and its metabolite increased with dose. The extrapolated partial area under the curve determined using the 24-hour concentration-time profile (AUC_{24}) obtained from this study at steady state appeared to be similar to the AUC_{24} for healthy subjects.