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

PROTOCOL NO.: 3180A1-200-WW

PROTOCOL TITLE: A 24-Week, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of the Safety and Efficacy of PPM-204 in Subjects With Type 2 Diabetes

Study Centers: A total of 57 centers took part in the study and 38 centers randomized subjects; 8 in the United States; 5 in India, 4 each in Mexico, Ukraine and Russia;; 3 each in Australia and Canada; ; 2 each in Serbia and Croatia; and 1 each in Hongkong, Italy and South Africa.

Study Initiation and Final Completion Dates: January 2007 to December 2007
The study was terminated prematurely based on predetermined futility criteria.

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- To identify doses of PPM-204 that were therapeutically effective and well tolerated in improving glycemic control over 24 weeks of treatment in subjects with type 2 diabetes mellitus (T2DM).

Secondary Objectives:

- To examine the effects of PPM-204 on body weight;
- To examine the effects of PPM-204 on plasma lipids;
- To examine the sources of variability in the plasma concentrations of PPM-204 using population pharmacokinetic (PK) methods.

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled study of PPM-204, with a comparator group (pioglitazone, 30 mg) in subjects with T2DM. The study consisted of the following 3 phases:

- A run-in/screening phase lasting 3 weeks, during which all previous antidiabetic medications were discontinued on the day of the Week -3 Visit; in this phase, subjects received single-blind placebo;

- A 24-week treatment phase, during which other antidiabetic drugs were not permitted. Subjects randomized to the placebo group received placebo only for the first 12 weeks, followed by double-blinded pioglitazone (30 mg) for the final 12 weeks of treatment.

- A 2-week post-treatment phase.

This study employed a 2-stage adaptive design:

In Stage 1, subjects were equally allocated to placebo, pioglitazone (30 mg), and PPM-204 (30 and 60 mg) up to a maximum of 240 subjects.

In Stage 2, subjects were to be allocated to placebo, pioglitazone (30 mg), and PPM-204 (15, 30, 60, and 120 mg). Enrollment in the 120-mg cohort was conditional on evidence of safety obtained during Stage 1 and enrollment in the 15-mg dose was contingent on evidence of efficacy obtained at the PPM-204 30-mg dose.

Subjects participated in the study for approximately 29 weeks.

Table 1. Study Flowchart

Study Procedures[a]	Week -3	Week -1	Day 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	Early Term	FU[b]
	3-Week Run-In												2-Week FU
Informed consent	X												
Inclusion/exclusion criteria	X	X											
Demography, medical history	X												
Physical examination	X[c]	X[d]	X[d, e]	X[d]	X[d]	X[d]	X[d]	X[d, e]	X[d]	X[d]	X[e]	X[e]	
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	
Edema assessment			X	X	X	X	X	X	X	X	X	X	
Electrocardiogram			X								X	X	
Full Lab evaluation[g]	X		X					X			X	X	
Limited Lab evaluation[h]				X	X	X	X		X	X			
FPG		X	X	X	X	X	X	X	X	X	X	X	
HbA1c	X	X						X			X	X	
Insulin, FFA			X	X				X			X	X	
Lipoproteins[i]			X					X			X	X	
FSH[j], TSH	X												
Adiponectin, hs-CRP			X					X			X	X	
Cyst-C, NT-proBNP, Tp-I			X		X		X	X	X		X	X	
HCV, hepatitis B tests	X												
Diet/exercise instruction	X		X				X		X				
PK sample collection			X		X		X[k]	X[k]	X[k]	X	X	X	
Dispense study drug.			X		X		X	X	X	X			
Dispense single-blind PBO	X												
Study drug accountability			X		X		X						
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X

BMI = body mass index; CBC = complete blood count; Cyst-C = Cystatin-C; FFA = Free fatty Acids; FPG = fasting plasma glucose; FSH = follicular stimulating hormone; FU = follow-up; HbA1c = glycosylated hemoglobin; HCV = Hepatitis C virus; HDL-C = High-density lipoprotein; hs-CRP = High sensitivity CRP; Lab = laboratory; NT-proBNP = N-terminal fragment of Brain Natriuretic Peptide; PBO = placebo; PK = pharmacokinetic; TC = Total cholesterol; TG = Triglycerides; Tp-I=Troponin-I; TSH = thyroid stimulating hormone.

a. A visit window of ±3 days was permitted from the Week –3 to the Week 6 visit; thereafter a visit window of ±4 days was permitted for all visits up to Week 24.
b. Approximately 2 weeks after the last dose of test article. The visit was performed by telephone, when appropriate. If AEs or clinical lab abnormalities were not adequately resolved at the time of the FU visit, additional FU visits were performed as appropriate.
c. Includes measurement of height.
d. Only brief physical assessment: included weight (kg), cardiovascular, respiratory systems.

Table 1. Study Flowchart

e. Add waist measurement.
f. BMI determination at the Week –3 visit. Sitting blood pressure and pulse rate after resting at least 5 minutes and oral/tympanic temperature (°C).
g. Blood chemistry with basic lipid panel (TC, TG, HDL-C, LDL-C, non-HDL-C, TC/HDL-C), hematology (CBC), urinalysis, including microalbumin and urinary creatinine.
h. Including blood chemistry with basic lipid panel (TC, TG, HDL-C, LDL-C, non-HDL-C, TC/HDL-C), hematology (CBC), urinalysis.
i. Apolipoprotein A-I, apolipoprotein B.
j. Only if required to determine postmenopausal state.
k. Post-dose PK sample collection at selected sites and for subjects who had agreed to the post-dose sample collection; this procedure was performed at the Week 8, Week 12 or Week 16 visit.

Number of Subjects (Planned and Analyzed): A total of 500 subjects were planned for the study. A total of 590 subjects entered the screening phase of this study (183 in the United States, 95 in India, 64 in Mexico, 43 in Ukraine, 41 each in Russia and Canada, 29 in Australia, 25 in Croatia, 24 in Hongkong, 16 in South Africa, 14 in Serbia, 10 in Italy, 4 in Romania and 1 in the United kingdom). A total of 219 subjects were randomly assigned and 218 subjects entered the treatment phase (54 to PPM-204 60 mg, 54 to PPM-204 30 mg, 55 to pioglitazone and 55 to placebo).

Diagnosis and Main Criteria for Inclusion: Men and women of non-childbearing potential, with T2DM, aged 18 to 70 years old; subjects currently treated with diet and exercise alone and subjects receiving a single oral antidiabetic medication, and having a body mass index >23 and <43 were eligible for the study. For subjects receiving 1 antidiabetic medication: glycosylated hemoglobin (HbA1c) was required to be ≥6.8% and ≤8.5%; for subjects not receiving antidiabetic medications: HbA1c was required to be ≥7.2% and ≤9.0%.

Main Criteria for Exclusion: Subjects requiring insulin therapy; receiving ≥2 oral antidiabetic medications; requiring systemic corticosteroids, unless treatment was discontinued at least 4 weeks before the screening visit; receiving warfarin; receiving thiazolidinediones, unless treatment was discontinued 8 weeks before the screening visit; and subjects with significant diabetic complications (retinopathy, nephropathy, symptomatic neuropathy) were excluded from the study.

Study Treatment: PPM-204 was provided as oral 30-mg and 60-mg capsules. Placebo capsules to match PPM-204, placebo capsules to match the comparator pioglitazone, and comparator pioglitazone capsules were administered orally.

Subjects were randomly assigned to 1 of the following treatment groups:

- PPM-204 30 mg;
- PPM-204 60 mg;
- Pioglitazone 30 mg;
- Placebo, for the initial 12 weeks (followed by pioglitazone 30 mg for the final 12 weeks of the treatment phase).

Subjects took oral test article daily during the run-in and treatment phase, in the morning before breakfast, at approximately the same time each day. During the 3-week run-in period, each subject received single-blind placebo.

Efficacy Endpoints:

Primary Efficacy Endpoints:

- To compare the mean changes of fasting plasma glucose (FPG) from Baseline/Day 1 to Week 12 among the PPM-204 active treatment groups and placebo. A normal dynamic linear model was used to estimate the FPG dose-response.

Secondary Efficacy Endpoints (at Week 12 and Week 24):

- Mean changes of HbA1c from Baseline among the PPM-204 active treatment groups and pioglitazone; mean changes of FPG at Week 24;
- Fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and quantitative insulin sensitivity check index (QUICKI) indices;
- Body weight, waist measurement;
- Total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total/HDL, apolipoprotein A-I, apolipoprotein B, triglycerides (TGs), free fatty acid (FFA);
- High sensitivity (hs) C-reactive protein;
- Adiponectin;
- Incidence of edema;
- Percentage of subjects with HbA1c $\leq$7.0% at Week 24;
- Percentage of subjects who met the escape criteria for hyperglycemia during the treatment phase.

Safety Evaluations: It included the results of spontaneously reported signs and symptoms (including hypoglycemia and hyperglycemia), scheduled physical examination findings including body weight, dedicated peripheral edema assessment, vital sign measurements, 12-lead electrocardiogram (ECG) determination, and clinical laboratory evaluations. Standard safety laboratory evaluations were performed at every study visit. In addition, Brain Natriuretic Peptide (eg, NT-proBNP), Troponin I and Cystatin-C were measured throughout the study. NT-proBNP was used as a biomarker for volume expansion and to assess the risk of developing or worsening heart failure. Troponin I was used to monitor for myocardial damage. Cystatin-C was used as an additional biomarker of renal function in addition to serum creatinine (SCr).

Statistical Methods:

Modified Intent-to-Treat (mITT) Population: Defined as all randomly assigned subjects who took at least 1 dose of test article and had a Baseline efficacy measurement and at least 1 post-baseline efficacy measurement. Efficacy analysis was based on the mITT population.

Safety Population: Defined as all randomly assigned subjects who took at least 1 dose of test article. Safety analysis was based on the safety population.

Continuous endpoints, eg, FPG, body weight, serum creatinine, total cholesterol, LDL-C, HDL-C, TGs, etc expressed as the change from Baseline, were analyzed using an analysis of covariance (ANCOVA) with treatment as a factor and Baseline as a covariate at each post-baseline time point.

All tests were performed as a 2-sided test with significance level α=0.05. There were no formal Type 1 error adjustments for multiple comparisons among the treatment groups. Descriptive statistics were also provided for the changes from Baseline for each variable.

RESULTS

Subject Disposition and Demography: A total of 218 subjects (117 men and 101 women) aged 30 to 70 years, with a median age of 55.0 years were randomly assigned and entered the treatment phase. One (1) additional subject was randomly assigned but received no active study medication.

One hundred and eighty-three (183) subjects withdrew from the study. Most discontinuations (136 of 183 subjects) were due to the Sponsor's request because of study termination. Subject participation is summarized in Table 2.

Table 2. Conclusion of Subject Participation Summary (Safety Population)

Conclusion Status Reason[a]	Treatment			
	PPM-204 60 mg N=54	PPM-204 30 mg N=54	Pioglitazone N=55	Placebo/Pioglitazone N=55
Total	54 (100)	54 (100)	55 (100)	55 (100)
Completed	6 (11.1)	11 (20.4)	9 (16.4)	9 (16.4)
Study completed	6 (11.1)	11 (20.4)	9 (16.4)	9 (16.4)
Discontinued	48 (88.9)	43 (79.6)	46 (83.6)	46 (83.6)
Adverse Event	3 (5.6)	1 (1.9)	3 (5.5)	5 (9.1)
Discontinuation of study by Sponsor	32 (59.3)	35 (64.8)	39 (70.9)	30 (54.5)
Lost to follow-up	5 (9.3)	0	1 (1.8)	3 (5.5)
Other	1 (1.9)	0	0	0
Protocol violation	0	0	1 (1.8)	1 (1.8)
Subject request	2 (3.7)	2 (3.7)	1 (1.8)	1 (1.8)
Unsatisfactory response - efficacy	5 (9.3)	5 (9.3)	1 (1.8)	6 (10.9)

N = number of subjects.
a. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.

Demographics are summarized in Table 3.

Table 3. Subject Demographics

Characteristics	Treatment			
	PPM-204 60 mg N=54	PPM-204 30 mg N=54	Pioglitazone N=55	Placebo/Pioglitazone N=55
Age (years)				
N	54	54	55	55
Mean	54.46	53.69	52.62	55.11
Standard deviation	7.76	10.20	8.01	9.00
Minimum	37.00	30.00	33.00	32.00
Maximum	70.00	68.00	70.00	69.00
Median	55.00	55.00	53.00	57.00
Sex, (n)				
Female	30 (55.56)	24 (44.44)	22 (40.00)	25 (45.45)
Male	24 (44.44)	30 (55.56)	33 (60.00)	30 (54.55)

N = number of subjects; n = number of subjects with specified criteria.

Efficacy Results:

Because of the early termination of the study not all endpoints were evaluated.

FPG: The changes from Baseline are shown in Table 4. At endpoint, after 12 weeks of treatment, FPG decreased by -7.4±5.1 mg/dL (mean ± SEM; number of subjects [n] =26) and -13.6±5.6 mg/dL (n=22), respectively, among subjects treated with PPM-204 (30 and 60 mg once daily [QD]). Among subjects treated with pioglitazone (30 mg QD), there was a decrease of -18.5±4.9 mg/dL (n=28); FPG was little affected in subjects treated with placebo (-3.4±5.7 mg/dL, n=21). The primary comparison of interest at endpoint (12 weeks) was versus placebo: only the decrease with pioglitazone was statistically significant ($p<0.05$).

After 24 weeks of treatment, subjects treated with pioglitazone showed a further decrease (-26.6±9.3 mg/dL; n=10); the decrease of FPG in the subjects treated with 60 mg PPM-204, was modest (-12.1±10.4 mg/dL; n=8); and subjects treated with 30 mg PPM-204 showed an increase of FPG (2.9±8.1 mg/dL; n=13). Subjects assigned to the placebo group received 30 mg pioglitazone after the 12-week visit in a double-blinded manner: introduction of active treatment after a 12-week washout period with placebo explains the robust decrease of FPG observed at the week-24 visit (-39.0±9.7 mg/dL; n=9).

Table 4. ANCOVA Results (Pioglitazone vs. PPM-204 Arms and Placebo/Pio Arm) (mITT Population)

Parameter: Fasting Plasma Glucose									
Timepoint	**Treatments**	**N**	**Raw Mean (SD)**	**N**	**Raw Change Mean (SD)**	**Adjusted Mean Change From Baseline (SE)**	**Difference of Adjusted Means Therapy-Pio (70% CI)**	**p-Value* vs Pio**	**Overall p-Value**
Baseline	Placebo/pio	51	167.5 (37.97)	-	-	-	-	-	-
	PPM-204 30 mg	54	170.7 (45.88)	-	-	-	-	-	-
	PPM-204 60 mg	54	165.9 (46.89)	-	-	-	-	-	-
	Pioglitazone	53	160.8 (41.55)	-	-	-	-	-	-
Week 12	Placebo/pio	21	155.2 (32.38)	21	-3.3 (21.56)	-3.4 (5.67)	-15.1 (-22.9, -7.2)	0.048	0.194
	PPM-204 30 mg	26	150.5 (39.60)	26	-7.1 (28.48)	-7.4 (5.09)	-11.1 (-18.5, -3.7)	0.122	
	PPM-204 60 mg	22	142.5 (33.56)	22	-12.5 (21.80)	-13.6 (5.55)	-4.9 (-12.7, 2.8)	0.510	
	Pioglitazone	29	144.6 (35.77)	28	-19.7 (33.74)	-18.5 (4.92)			
Week 24	Placebo/pio	9	116.6 (26.94)	9	-40.4 (24.58)	-39.0 (9.72)	12.4 (-1.7, 26.6)	0.362	0.013
	PPM-204 30 mg	13	157.6 (39.24)	13	3.3 (41.92)	2.9 (8.09)	-29.4 (-42.4,-16.5)	0.022	
	PPM-204 60 mg	8	145.8 (29.89)	8	-18.2 (24.63)	-12.1 (10.39)	-14.4 (-29.2, 0.3)	0.311	
	Pioglitazone	10	125.6 (20.43)	10	-21.1 (45.10)	-26.6 (9.30)			

*p-values obtained from general linear model: change from baseline = baseline + treatment.
CI = confidence interval; N = number of subjects; pio = Pioglitazone SD = standard deviation; SE = standard error; vs = versus.

HbA1c: At 12 weeks, neither subjects treated with 30 and 60 mg PPM-204 nor with pioglitazone showed a decrease of HbA1c from Baseline (PPM-204, 30 mg: -0.1±0.2%, n=25; PPM-204, 60 mg: +0.1±0.2%, n=21; pioglitazone: +0.1±0.2%, n=30). In subjects treated with placebo, HbA1c increased moderately (+0.3±0.2%, n=21) (Table 5). The following 2 factors might have contributed to confound and minimize treatment effects on HbA1c. First, before randomization, most of the subjects were treated with an oral antidiabetic drug (70 to 75 %): because of the short duration of the washout period (3 weeks), HbA1c levels were far from steady state at Baseline. Second, 12 weeks might be too short a treatment duration for peroxisome proliferation-activated receptor (PPAR) agonists to show a full therapeutic effect.

After 24 weeks of treatment, HbA1c increased by +0.3±0.3% (n=13) in subjects treated with 30 mg PPM-204 and did not change (0.0±0.3%; n=8) in subjects treated with 60 mg PPM-204. Among subjects treated with pioglitazone, HbA1c decreased by -0.5±0.3% (n=10). Subjects randomly assigned with placebo received 30 mg pioglitazone after the Week 12 visit: HbA1c decreased by -0.6±0.3% (n=9).

Table 5. ANCOVA Results (Pioglitazone vs. PPM-204 Arms and Placebo/Pio Arm) (mITT Population)

Parameter: HbA1c (L/L)									
Timepoint	**Treatments**	**N**	**Raw Mean (SD)**	**N**	**Raw Change Mean (SD)**	**Adjusted Mean Change From Baseline (SE)**	**Difference of Adjusted Means Therapy-Pio (70% CI)**	**p-Value* vs Pio**	**Overall p-Value**
Baseline	Placebo/pio	53	0.077 (0.0062)						
	PPM-204 30 mg	54	0.077 (0.0061)						
	PPM-204 60 mg	53	0.078 (0.0057)						
	Pioglitazone	54	0.077 (0.0052)						
Week 12	Placebo/pio	21	0.078 (0.0093)	21	0.003 (0.0107)	0.003 (0.0023)	-.002 (-.005,0.001)	0.478	0.763
	PPM-204 30 mg	25	0.075 (0.0121)	25	-.000 (0.0103)	-.001 (0.0021)	0.001 (-.002,0.004)	0.680	
	PPM-204 60 mg	22	0.077 (0.0120)	21	0.000 (0.0130)	0.001 (0.0023)	0.000 (-.003,0.003)	0.991	
	Pioglitazone	30	0.077 (0.0106)	30	0.000 (0.0098)	0.001 (0.0020)			
Week 24	Placebo/pio	9	0.071 (0.0054)	9	-.007 (0.0080)	-.006 (0.0033)	0.001 (-.004,0.006)	0.877	0.111
	PPM-204 30 mg	13	0.078 (0.0121)	13	0.004 (0.0108)	0.003 (0.0027)	-.008 (-.013,-.004)	0.050	
	PPM-204 60 mg	8	0.077 (0.0129)	8	-.001 (0.0139)	0.000 (0.0035)	-.006 (-.011,-.001)	0.253	
	Pioglitazone	10	0.070 (0.0071)	10	-.004 (0.0056)	-.005 (0.0031)			

*p-values obtained from general linear model: change from Baseline = baseline + treatment.
CI = confidence interval; HbA1c = glycosylated hemoglobin; mITT = modified intent-to-treat; N = number of subjects; pio = pioglitazone; SD = standard deviation; SE = standard error; vs = versus.

Body Weight: After 12 weeks of treatment, subjects treated with 30 and 60 mg PPM-204 did not gain weight compared with placebo-treated subjects (30 mg PPM-204: -0.9±0.5 kg, n=26; 60 mg PPM-204: -0.4±0.6 kg, n=22; placebo: -0.8±0.6 kg, n=21; p>0.05 for each comparison) (Table 6). Among subjects treated with pioglitazone there was a statistically significant increase versus placebo (+1.5±0.5 kg; n=30) (p<0.05). The increase in weight for the pioglitazone group was also statistically significant versus 30 mg PPM-204 (p=0.001) and 60 mg PPM-204 (p=0.016).

After 24 weeks of treatment, the average weight of subjects treated with 30 and 60 mg PPM-204 remained stable (PPM-204, 30 mg: -0.8±1.4 kg, n=13; PPM-204, 60 mg: +0.3±1.8 kg, n=8), while the weight of subjects treated with pioglitazone further increased (+3.1±1.6 kg; n=10). Subjects randomly assigned to the placebo group received 30 mg pioglitazone after the 12-week visit: the average weight increase from Baseline was +0.9±1.6 kg, n=9.

Total Cholesterol: The results of total cholesterol in subjects treated with 30 and 60 mg PPM-204 are summarized in (Table 7).

LDL: None of the treatment groups (Table 8) demonstrated a major effect (p>0.05) on LDL after 12 weeks of treatment (PPM-204, 30 mg: -0.12±0.10 mmol/L, n=25; PPM-204, 60 mg: +0.10±0.11 mmol/L, n=21; pioglitazone: +0.14±0.09 mmol/L, n=28; placebo 0.05±0.11 mmol/L, n=19).

HDL: Both PPM-204 and pioglitazone produced a modest increase of HDL concentration (Table 9) and (Table 10) from baseline after 12 weeks (PPM-204, 30 mg; +0.04±0.03 mmol/L, n=25; PPM-204, 60 mg: + 0.11±0.04 mmol/L, n=21; pioglitazone: +0.14±0.03 mmol/L, n=28). Only the increase with pioglitazone was statistically significant versus placebo (p<0.05). In subjects treated with placebo for 12 weeks, HDL increased modestly (+0.03±0.04 mmol/L, n=19).

Table 6. ANCOVA Results (Pioglitazone vs. PPM-204 Arms and Placebo/Pio Arm) (mITT Population)

Parameter: Body Weight (kg)									
Timepoint	**Treatments**	**N**	**Raw Mean (SD)**	**N**	**Raw Change Mean (SD)**	**Adjusted Mean Change From Baseline (SE)**	**Difference of Adjusted Means Therapy-Pio (70% CI)**	**p-Value* vs Pio**	**Overall p-Value**
Baseline	Placebo/pio	53	76.9 (15.25)						
	PPM-204 30 mg	54	81.7 (16.32)						
	PPM-204 60 mg	54	77.5 (15.20)						
	Pioglitazone	55	80.7 (17.78)						
Week 12	Placebo/pio	21	80.1 (18.38)	21	-0.8 (1.76)	-0.8 (0.60)	2.3 (1.5, 3.1)	0.004	0.004
	PPM-204 30 mg	26	85.3 (15.07)	26	-1.0 (3.95)	-0.9 (0.54)	2.5 (1.7, 3.3)	0.001	
	PPM-204 60 mg	22	74.7 (14.55)	22	-0.2 (2.47)	-0.4 (0.59)	1.9 (1.1, 2.7)	0.016	
	Pioglitazone	30	82.0 (19.49)	30	1.6 (2.16)	1.5 (0.50)			
Week 24	Placebo/pio	9	84.7 (22.99)	9	0.8 (2.19)	0.9 (1.65)	2.2 (-0.2, 4.6)	0.339	0.331
	PPM-204 30 mg	13	83.4 (18.46)	13	-0.9 (6.91)	-0.8 (1.38)	3.9 (1.7, 6.1)	0.072	
	PPM-204 60 mg	8	73.9 (10.03)	8	0.6 (3.56)	0.3 (1.78)	2.8 (0.3, 5.3)	0.246	
	Pioglitazone	10	87.1 (27.18)	10	3.0 (4.48)	3.1 (1.57)			

* p-values obtained from general linear model: change from Baseline = baseline + treatment.
CI = confidence interval; mITT = modified Intent-to-treat; N = number of subjects; pio = pioglitazone; SD = standard deviation; SE = standard error; vs = versus.

Table 7. ANCOVA Results (Pioglitazone vs. PPM-204 Arms and Placebo/Pio Arm) (mITT Population)

Parameter: Total Cholesterol (mmol/L)									
Timepoint	**Treatments**	**N**	**Raw Mean (SD)**	**N**	**Raw Change Mean (SD)**	**Adjusted Mean Change from Baseline (SE)**	**Difference of Adjusted Means Therapy-Pio (70% CI)**	**p-Value* vs Pio**	**Overall p-Value**
Baseline	Placebo/pio	50	4.94 (1.026)						
	PPM-204 30 mg	53	5.14 (1.092)						
	PPM-204 60 mg	52	4.94 (1.057)						
	Pioglitazone	52	4.78 (1.090)						
Week 12	Placebo/pio	21	4.83 (0.893)	19	0.20 (0.529)	0.19 (0.144)	0.18 (-0.01, 0.37)	0.337	0.104
	PPM-204 30 mg	26	4.50 (0.973)	25	-0.06 (0.559)	-0.07 (0.125)	0.43 (0.25, 0.61)	0.014	
	PPM-204 60 mg	22	5.13 (0.971)	21	0.12 (0.620)	0.18 (0.138)	0.19 (-0.00, 0.38)	0.305	
	Pioglitazone	30	4.84 (1.099)	28	0.40 (0.793)	0.37 (0.119)			
Week 24	Placebo/pio	9	5.00 (1.070)	8	0.45 (0.584)	0.40 (0.259)	0.04 (-0.33, 0.41)	0.914	0.752
	PPM-204 30 mg	13	4.62 (1.280)	12	0.20 (0.384)	0.19 (0.209)	0.25 (-0.09, 0.58)	0.444	
	PPM-204 60 mg	8	5.71 (1.243)	8	0.45 (0.524)	0.54 (0.266)	-0.09 (-0.48, 0.29)	0.797	
	Pioglitazone	10	4.91 (1.153)	9	0.46 (1.194)	0.44 (0.242)			

* p-values obtained from general linear model: change from Baseline = baseline + treatment.
CI = confidence interval; mITT = modified Intent-to-treat; N = number of subjects; pio = pioglitazone; SD = standard deviation; SE = standard error; vs = versus.

Table 8. ANCOVA Results (Pioglitazone vs. PPM-204 Arms and Placebo/Pio Arm) (mITT Population)

Parameter: LDL-C (mmol/L)									
Timepoint	**Treatments**	**N**	**Raw Mean (SD)**	**N**	**Raw Change Mean (SD)**	**Adjusted Mean Change From Baseline (SE)**	**Difference of Adjusted Means Therapy-Pio (70% CI)**	**p-Value* vs Pio**	**Overall p-Value**
Baseline	Placebo/pio	50	3.00 (0.853)						
	PPM-204 30 mg	53	3.22 (1.003)						
	PPM-204 60 mg	52	3.03 (0.925)						
	Pioglitazone	52	2.93 (0.824)						
Week 12	Placebo/pio	21	3.01 (0.777)	19	0.05 (0.539)	0.05 (0.111)	0.09 (-0.06, 0.24)	0.534	0.252
	PPM-204 30 mg	26	2.63 (0.822)	25	-0.08 (0.479)	-0.12 (0.097)	0.26 (0.12, 0.40)	0.056	
	PPM-204 60 mg	22	3.26 (0.861)	21	0.03 (0.573)	0.10 (0.106)	0.04 (-0.10, 0.19)	0.768	
	Pioglitazone	30	2.97 (0.793)	28	0.16 (0.519)	0.14 (0.091)			
Week 24	Placebo/pio	9	3.13 (0.934)	8	0.25 (0.574)	0.19 (0.186)	-0.04 (-0.31, 0.23)	0.878	0.510
	PPM-204 30 mg	13	2.61 (1.010)	12	-0.01 (0.308)	-0.03 (0.151)	0.18 (-0.06, 0.43)	0.427	
	PPM-204 60 mg	8	3.48 (1.016)	8	0.23 (0.471)	0.32 (0.188)	-0.17 (-0.44, 0.10)	0.502	
	Pioglitazone	10	3.02 (0.774)	9	0.14 (0.831)	0.15 (0.173)			

* p-values obtained from general linear model: change from Baseline = baseline + treatment.
CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; mITT = modified Intent-to-treat; N = number of subjects; pio = pioglitazone; SD = standard deviation; SE = standard error; vs = versus.

Table 9. ANCOVA Results (Pioglitazone vs. PPM-204 Arms and Placebo/Pio Arm) (mITT Population)

Parameter: HDL-C (mmol/L)									
Timepoint	**Treatments**	**N**	**Raw Mean (SD)**	**N**	**Raw Change Mean (SD)**	**Adjusted Mean Change From Baseline (SE)**	**Difference of Adjusted Means Therapy-Pio (70% CI)**	**p-Value* vs Pio**	**Overall p-Value**
Baseline	Placebo/pio	50	1.11 (0.270)						
	PPM-204 30 mg	53	1.23 (0.336)						
	PPM-204 60 mg	52	1.25 (0.318)						
	Pioglitazone	52	1.10 (0.239)						
Week 12	Placebo/pio	21	1.12 (0.287)	19	0.05 (0.117)	0.03 (0.040)	0.11 (0.06,0.16)	0.033	0.077
	PPM-204 30 mg	26	1.30 (0.348)	25	0.02 (0.239)	0.04 (0.035)	0.10 (0.05,0.15)	0.042	
	PPM-204 60 mg	22	1.31 (0.345)	21	0.10 (0.182)	0.11 (0.038)	0.03 (-.03,0.08)	0.595	
	Pioglitazone	30	1.24 (0.260)	28	0.16 (0.166)	0.14 (0.033)			
Week 24	Placebo/pio	9	1.22 (0.417)	8	0.14 (0.235)	0.12 (0.076)	-.06 (-0.17,0.05)	0.550	0.534
	PPM-204 30 mg	13	1.34 (0.400)	12	0.02 (0.183)	0.04 (0.062)	0.02 (-.08,0.13)	0.833	
	PPM-204 60 mg	8	1.55 (0.295)	8	0.14 (0.315)	0.17 (0.077)	-.11 (-.23,0.01)	0.323	
	Pioglitazone	10	1.11 (0.161)	9	0.09 (0.090)	0.06 (0.074)			

*p-values obtained from general linear model: change from Baseline = baseline + treatment.
CI = confidence interval; HDL-C = High-density lipoprotein cholesterol; mITT = modified Intent-to-treat; N = number of subjects; pio = pioglitazone; SD = standard deviation; SE = standard error; vs = versus.

Table 10. ANCOVA Results (Pioglitazone vs. PPM-204 Arms and Placebo/Pio Arm) (mITT Population)

Parameter: HDL Ratio									
Timepoint	**Treatments**	**N**	**Raw Mean (SD)**	**N**	**Raw Change Mean (SD)**	**Adjusted Mean Change From Baseline (SE)**	**Difference of Adjusted Means Therapy-Pio (70% CI)**	**p-Value* vs Pio**	**Overall p-Value**
Baseline	Placebo/pio	50	4.70 (1.574)						
	PPM-204 30 mg	53	4.35 (1.123)						
	PPM-204 60 mg	52	4.14 (1.153)						
	Pioglitazone	52	4.52 (1.445)						
Week 12	Placebo/pio	21	4.52 (1.332)	19	0.00 (0.685)	0.03 (0.167)	-0.19 (-0.42, 0.03)	0.373	0.769
	PPM-204 30 mg	26	3.74 (1.416)	25	-0.09 (0.649)	-0.13 (0.146)	-0.04 (-0.25, 0.17)	0.846	
	PPM-204 60 mg	22	4.14 (1.152)	21	-0.20 (0.746)	-0.20 (0.158)	0.03 (-0.19, 0.25)	0.878	
	Pioglitazone	30	4.07 (1.252)	28	-0.17 (0.807)	-0.16 (0.137)			
Week 24	Placebo/pio	9	4.38 (1.409)	8	-0.06 (0.691)	-0.05 (0.317)	0.16 (-0.30, 0.62)	0.716	0.970
	PPM-204 30 mg	13	3.66 (1.395)	12	0.15 (0.623)	0.13 (0.263)	-0.02 (-0.45, 0.42)	0.968	
	PPM-204 60 mg	8	3.83 (1.121)	8	0.03 (0.888)	0.01 (0.317)	0.10 (-0.37, 0.57)	0.825	
	Pioglitazone	10	4.55 (1.431)	9	0.08 (1.252)	0.11 (0.306)			

* p-values obtained from general linear model: change from Baseline = baseline + treatment.
CI = confidence interval; HDL = high-density lipoprotein; mITT = modified Intent-to-treat; N = number of subjects; pio pioglitazone; SD = standard deviation; SE = standard error; vs = versus.

TGs: After 12 weeks, subjects (Table 11) treated with PPM-204 (30 and 60 mg) had a modest decrease of TGs (30 mg PPM-204:-0.13±0.16 mmol/L, n=25; 60 mg PPM-204: -0.16±0.18 mmol/L, n=21). TGs did not change in subjects treated with pioglitazone (0.01±0.15 mmol/L; n=28) and increased in subjects treated with placebo (0.30±0.19 mmol/L; n=19). None of these changes were statistically significant.

Adiponectin: In subjects treated with 30 and 60 mg PMM-204 (Table 12) there was a moderate increase in the concentration of adiponectin after 12 weeks of treatment (30 mg PPM-204: +3.90±1.42 µg/mL, n=25 [$p<0.05$]; 60 mg PPM-204: +3.19±1.52 µg/mL; n=22 [$p>0.05$]). Adiponectin concentration decreased in subjects treated with placebo (-1.09±1.55 µg/mL, n=21). Treatment with pioglitazone produced a robust increase of adiponectin (+10.03±1.29 µg/mL, n=30; $p<0.05$).

After 24 weeks of treatment, adiponectin concentration increased by +4.76±3.40 µg/mL, n=9 in subjects treated with placebo/pioglitazone. Adiponectin also increased in subjects treated with PPM-204 30 and 60 mg (+7.40±2.82, n=13 and +4.13±3.59 µg/mL, n=8, respectively). Adiponectin remained elevated and did not further increase in subjects treated with pioglitazone (+9.73±3.23 µg/mL, n=10).

Table 11. ANCOVA Results (Pioglitazone vs. PPM-204 Arms and Placebo/Pio Arm) (mITT Population)

Parameter: Triglycerides (mmol/L)									
Timepoint	**Treatments**	**N**	**Raw Mean (SD)**	**N**	**Raw Change Mean (SD)**	**Adjusted Mean Change From Baseline (SE)**	**Difference of Adjusted Means Therapy-Pio (70% CI)**	**p-Value* vs Pio**	**Overall p-Value**
Baseline	Placebo/pio	50	2.36 (2.445)						
	PPM-204 30 mg	53	2.02 (1.012)						
	PPM-204 60 mg	52	2.04 (1.031)						
	Pioglitazone	52	2.24 (2.290)						
Week 12	Placebo/pio	21	2.12 (1.106)	19	0.29 (0.753)	0.30 (0.187)	-0.29 (-0.55,-0.04)	0.229	0.264
	PPM-204 30 mg	26	1.63 (0.945)	25	-0.13 (0.678)	-0.13 (0.163)	0.14 (-0.09, 0.37)	0.536	
	PPM-204 60 mg	22	1.74 (0.914)	21	-0.18 (0.953)	-0.16 (0.179)	0.17 (-0.08, 0.41)	0.484	
	Pioglitazone	30	1.70 (1.225)	28	0.02 (0.899)	0.01 (0.155)			
Week 24	Placebo/pio	9	1.62 (0.606)	8	-0.01 (0.619)	-0.03 (0.251)	0.58 (0.22, 0.95)	0.101	0.323
	PPM-204 30 mg	13	1.83 (1.722)	12	0.36 (0.945)	0.37 (0.205)	0.18 (-0.15, 0.51)	0.560	
	PPM-204 60 mg	8	1.91 (1.116)	8	0.15 (0.633)	0.09 (0.252)	0.47 (0.11, 0.84)	0.183	
	Pioglitazone	10	1.92 (1.365)	9	0.51 (0.764)	0.56 (0.237)			

* p-values obtained from general linear model: change from Baseline = baseline + treatment.
CI = confidence interval; mITT = modified Intent-to-treat; N = number of subjects; pio = pioglitazone; SD = standard deviation; SE = standard error; vs = versus.

Table 12. ANCOVA Results (Pioglitazone vs. PPM-204 Arms and Placebo/Pio Arm) (mITT Population)

Parameter: Adiponectin (mcg/mL)									
Timepoint	**Treatments**	**N**	**Raw Mean (SD)**	**N**	**Raw Change Mean (SD)**	**Adjusted Mean Change From Baseline (SE)**	**Difference of Adjusted Means Therapy-Pio (70% CI)**	**p-Value* vs Pio**	**Overall p-Value**
Baseline	Placebo/pio	50	7.12 (7.156)						
	PPM-204 30 mg	52	7.35 (4.320)						
	PPM-204 60 mg	52	6.37 (3.574)						
	Pioglitazone	54	6.15 (3.700)						
Week 12	Placebo/pio	21	6.71 (4.958)	21	-1.11 (4.451)	-1.09 (1.547)	11.12 (9.01, 13.22)	<.001	<.001
	PPM-204 30 mg	25	12.23 (10.232)	25	3.85 (6.638)	3.90 (1.423)	6.12 (4.11, 8.13)	0.002	
	PPM-204 60 mg	22	9.44 (6.278)	22	3.25 (3.499)	3.19 (1.517)	6.83 (4.76, 8.91)	<.001	
	Pioglitazone	30	16.93 (11.170)	30	10.05 (10.102)	10.03 (1.294)			
Week 24	Placebo/pio	9	15.73 (14.811)	9	5.09 (8.949)	4.76 (3.404)	4.96 (-0.02, 9.94)	0.302	0.623
	PPM-204 30 mg	13	17.36 (16.387)	13	7.57 (13.572)	7.40 (2.820)	2.32 (-2.21, 6.86)	0.593	
	PPM-204 60 mg	8	11.56 (4.849)	8	3.92 (3.128)	4.13 (3.594)	5.60 (0.53, 10.66)	0.253	
	Pioglitazone	10	16.26 (12.137)	10	9.38 (9.101)	9.73 (3.235)			

* p-values obtained from general linear model: change from Baseline = baseline + treatment.
CI = confidence interval; mITT = modified Intent-to-treat; N = number of subjects; pio = pioglitazone; SD = standard deviation; SE = standard error; vs = versus.

Safety Results:

Incidence of Edema: The percentage of subjects reporting edema of any severity with 30 and 60 mg PPM-204 was not different, or lower, than with placebo. At the 12-week visit, 9.5% (2/21) of the subjects treated with placebo reported edema versus 3.8% (1/26) and 0% (0/22) of the subjects treated with 30 and 60 mg PPM-204, respectively. Incidence of edema was higher (4/30, 13.3%) in subjects treated with pioglitazone. The difference was not statistically significant. The number of subjects at later time points is too low to allow meaningful comparisons. The number and percentage of subjects with treatment-emergent edema events is summarized in Table 13.

Table 13. Descriptive Statistics and Analysis Within and Between Treatments for Vital Signs and Physical Characteristics: Incidence of Edema

EDEMA Data Analysis Interval	Overall p-Value	Treatments				Total
		Placebo/ Pioglitazone	PPM-204 30 mg	PPM-204 60 mg	Pioglitazone	
Total	0.843	5/54 (9.3)	4/54 (7.4)	3/54 (5.6)	6/55 (10.9)	18/217 (8.3)
Week 2	0.394	0/53 (0.0)	2/52 (3.8)	1/50 (2.0)	3/53 (5.7)	6/208 (2.9)
Week 4	0.708	1/44 (2.3)	1/45 (2.2)	1/41 (2.4)	0/48 (0.0)	3/178 (1.7)
Week 6	0.085	3/32 (9.4)	0/40 (0.0)	0/36 (0.0)	2/40 (5.0)	5/148 (3.4)
Week 8	0.311	4/25 (16.0)	1/32 (3.1)	1/28 (3.6)	2/33 (6.1)	8/118 (6.8)
Week 12	0.301	2/21 (9.5)	1/26 (3.8)	0/22 (0.0)	4/30 (13.3)	7/99 (7.1)
Week 16	0.193	1/15 (6.7)	0/20 (0.0)	0/15 (0.0)	3/ 22 (13.6)	4/72 (5.6)
Week 20	0.846	1/12 (8.3)	0/14 (0.0)	0/11 (0.0)	1/14 (7.1)	2/51 (3.9)
Week 24	0.550	1/9 (11.1)	0/13 (0.0)	0/8 (0.0)	1/10 (10.0)	2/40 (5.0)
Follow-up	0.812	1/9 (11.1)	0/11 (0.0)	1/12 (8.3)	0/6 (0.0)	2/38 (5.3)

* Overall p-value: Fisher's exact test p-value (2-tail).

Serum Creatinine: After 12 weeks, SCr was not different from Baseline in each of the 4 treatment groups (30 mg PPM-204: -0.2±1.7 µmol/L, n=25; PPM-204, 60 mg: +1.0±1.8 µmol/L, n=21; pioglitazone: -1.0±1.6 µmol/L, n=28; placebo: +2.1±1.9 µmol/L, n=19) (Table 14).

After 24 weeks of treatment, SCr increased in all 4 treatment groups (30 mg PPM-204: +0.6±2.6 µmol/L, n=12; PPM-204, 60 mg: +10.0±3.2 µmol/L, n=8; pioglitazone: +2.9±3.0 µmol/L, n=9; placebo: +6.7±3.2 µmol/L, n=8). None of these changes was statistically significant.

Table 14. ANCOVA Results (Pioglitazone vs. PPM-204 Arms and Placebo/Pio Arm) (mITT Population)

Parameter: Serum Creatinine (umol/L)									
Timepoint	**Treatments**	**N**	**Raw Mean (SD)**	**N**	**Raw Change Mean (SD)**	**Adjusted Mean Change from Baseline(SE)**	**Difference of Adjusted Means Therapy-Pio (70% CI)**	**p-Value* vs Pio**	**Overall p-Value**
Baseline	Placebo/pio	50	75.3 (16.29)						
	PPM-204 30 mg	53	74.4 (12.51)						
	PPM-204 60 mg	52	70.5 (15.73)						
	Pioglitazone	52	72.5 (16.51)						
Week 12	Placebo/pio	21	78.0 (14.06)	19	1.9 (7.57)	2.1 (1.95)	-3.1 (-5.7, -0.5)	0.222	0.626
	PPM-204 30 mg	26	75.9 (13.62)	25	-0.4 (9.46)	-0.2 (1.70)	-0.8 (-3.3, 1.6)	0.726	
	PPM-204 60 mg	22	73.6 (17.90)	21	1.3 (8.98)	1.0 (1.85)	-2.0 (-4.6, 0.5)	0.405	
	Pioglitazone	30	74.6 (21.62)	28	-0.9 (8.53)	-1.0 (1.60)			
Week 24	Placebo/pio	9	76.9 (13.22)	8	6.8 (6.36)	6.7 (3.23)	-3.9 (-8.5, 0.8)	0.391	0.143
	PPM-204 30 mg	13	72.9 (18.53)	12	0.7 (10.41)	0.6 (2.64)	2.2 (-2.0, 6.5)	0.581	
	PPM-204 60 mg	8	78.5 (26.53)	8	10.0 (8.94)	10.0 (3.23)	-7.2 (-11.8, -2.5)	0.117	
	Pioglitazone	10	83.0 (34.39)	9	2.9 (8.92)	2.9 (3.04)			

* p-values obtained from general linear model: change from Baseline = baseline + treatment.
CI = confidence interval; mITT = modified Intent-to-treat; N = number of subjects; pio = pioglitazone; SD = standard deviation; SE = standard error; vs = versus.

Treatment-Emergent Adverse Events (TEAEs): Eighty-nine (89) subjects had TEAEs: 26 (47.3%) in the placebo group, 21 (38.9%) in the 30-mg PPM-204 group, 23 (42.6%) in the 60-mg PPM-204 group and 19 (34.5%) in the pioglitazone group. The most frequent TEAEs observed were urinary tract infection (12 subjects); headache (9 subjects); cough, influenza, and back pain (5 subjects each); and chest pain, anemia, constipation, sinusitis, peripheral edema, arthralgia, and myalgia (4 subjects, each). A summary of the number of subjects reporting TEAEs during the study is provided in Table 15.

Table 15. Number (%) of Subjects Who Reported Treatment-Emergent Adverse Events (Safety Population)

System Organ Class[a] Preferred Term	Treatment			
	PPM-204 60 mg N=54	PPM-204 30 mg N=54	Pioglitazone N=55	Placebo/Pioglitazone N=55
Any adverse event	23 (42.6)	21 (38.9)	19 (34.5)	26 (47.3)
Blood and lymphatic system disorders	1 (1.9)	2 (3.7)	1 (1.8)	2 (3.6)
Anaemia	1 (1.9)	2 (3.7)	1 (1.8)	0
Iron deficiency anaemia	0	0	0	1 (1.8)
Lymphadenitis	0	0	0	1 (1.8)
Cardiac disorders	2 (3.7)	1 (1.9)	1 (1.8)	0
Bradycardia	0	1 (1.9)	0	0
Coronary artery disease	1 (1.9)	0	0	0
Myocardial infarction	1 (1.9)	0	0	0
Supraventricular extrasystoles	1 (1.9)	0	1 (1.8)	0
Congenital, familial and genetic disorders	0	0	0	1 (1.8)
Type II hyperlipidaemia	0	0	0	1 (1.8)
Eye disorders	1 (1.9)	1 (1.9)	2 (3.6)	0
Cataract	1 (1.9)	1 (1.9)	0	0
Eyelid oedema	0	0	1 (1.8)	0
Glaucoma	0	1 (1.9)	0	0
Keratoconjunctivitis sicca	1 (1.9)	1 (1.9)	0	0
Ocular hypertension	0	1 (1.9)	0	0
Pinguecula	1 (1.9)	1 (1.9)	0	0
Punctate keratitis	1 (1.9)	1 (1.9)	0	0
Vision blurred	0	0	1 (1.8)	0
Gastrointestinal disorders	0	4 (7.4)	5 (9.1)	5 (9.1)
Abdominal pain	0	0	0	1 (1.8)
Abdominal pain lower	0	0	1 (1.8)	0
Abdominal tenderness	0	0	1 (1.8)	0
Constipation	0	3 (5.6)	1 (1.8)	0
Diarrhoea	0	0	0	1 (1.8)
Dyspepsia	0	0	1 (1.8)	0
Flatulence	0	0	1 (1.8)	0
Gingivitis	0	0	0	1 (1.8)
Irritable bowel syndrome	0	0	0	1 (1.8)
Nausea	0	0	1 (1.8)	1 (1.8)
Stomach discomfort	0	1 (1.9)	0	0
Toothache	0	0	1 (1.8)	0
General disorders and administration site conditions	3 (5.6)	2 (3.7)	4 (7.3)	4 (7.3)
Asthenia	0	1 (1.9)	0	1 (1.8)
Chest discomfort	0	1 (1.9)	0	0
Chest pain	2 (3.7)	0	0	2 (3.6)
Fatigue	0	1 (1.9)	0	1 (1.8)
Malaise	0	0	1 (1.8)	0
Oedema	1 (1.9)	0	0	0
Oedema peripheral	0	0	3 (5.5)	1 (1.8)
Immune system disorders	0	1 (1.9)	0	0
Seasonal allergy	0	1 (1.9)	0	0
Infections and infestations	12 (22.2)	10 (18.5)	7 (12.7)	9 (16.4)
Bronchitis	2 (3.7)	0	0	0
Cellulitis	1 (1.9)	0	0	0
Folliculitis	0	0	1 (1.8)	0
Gastroenteritis	1 (1.9)	0	0	0
Influenza	1 (1.9)	1 (1.9)	2 (3.6)	1 (1.8)
Laryngitis	0	1 (1.9)	0	0
Nasopharyngitis	0	2 (3.7)	0	1 (1.8)
Otitis media	0	0	0	1 (1.8)

Table 15. Number (%) of Subjects Who Reported Treatment-Emergent Adverse Events (Safety Population)

System Organ Class[a] Preferred Term	Treatment			
	PPM-204 60 mg N=54	PPM-204 30 mg N=54	Pioglitazone N=55	Placebo/Pioglitazone N=55
Pharyngitis	1 (1.9)	0	1 (1.8)	1 (1.8)
Sinusitis	1 (1.9)	0	1 (1.8)	2 (3.6)
Upper respiratory tract infection	2 (3.7)	3 (5.6)	0	1 (1.8)
Urinary tract infection	4 (7.4)	4 (7.4)	2 (3.6)	2 (3.6)
Injury, poisoning and procedural complications	3 (5.6)	3 (5.6)	0	1 (1.8)
Arthropod sting	1 (1.9)	0	0	0
Contusion	1 (1.9)	2 (3.7)	0	0
Joint sprain	1 (1.9)	0	0	0
Soft tissue injury	0	1 (1.9)	0	0
Traumatic haematoma	0	0	0	1 (1.8)
Investigations	3 (5.6)	3 (5.6)	4 (7.3)	4 (7.3)
Alanine aminotransferase increased	0	0	0	1 (1.8)
Blood bilirubin increased	0	1 (1.9)	0	0
Blood creatine phosphokinase increased	1 (1.9)	0	0	0
Blood creatinine increased	1 (1.9)	0	1 (1.8)	1 (1.8)
Blood urine present	0	0	0	1 (1.8)
Cardiac murmur	0	1 (1.9)	1 (1.8)	0
Crystal urine present	0	0	1 (1.8)	0
Electrocardiogram QT prolonged	0	0	0	1 (1.8)
Electrocardiogram T wave inversion	1 (1.9)	0	0	0
Glomerular filtration rate decreased	1 (1.9)	0	0	0
Weight decreased	1 (1.9)	0	0	0
Weight increased	0	1 (1.9)	1 (1.8)	0
Metabolism and nutrition disorders	3 (5.6)	2 (3.7)	1 (1.8)	4 (7.3)
Anorexia	0	1 (1.9)	0	0
Dyslipidaemia	0	0	1 (1.8)	1 (1.8)
Gout	1 (1.9)	0	0	0
Hypercholesterolaemia	0	0	0	1 (1.8)
Hyperglycaemia	0	0	0	1 (1.8)
Hyperlipidaemia	0	0	0	1 (1.8)
Hypertriglyceridaemia	0	1 (1.9)	0	0
Hypokalaemia	2 (3.7)	0	0	0
Hyponatraemia	1 (1.9)	0	0	0
Musculoskeletal and connective tissue disorders	7 (13.0)	6 (11.1)	3 (5.5)	7 (12.7)
Arthralgia	2 (3.7)	0	1 (1.8)	1 (1.8)
Arthritis	0	1 (1.9)	0	0
Back pain	2 (3.7)	0	1 (1.8)	2 (3.6)
Flank pain	0	1 (1.9)	0	0
Muscle contracture	0	0	0	1 (1.8)
Muscle spasms	0	1 (1.9)	0	0
Musculoskeletal chest pain	0	0	1 (1.8)	0
Myalgia	1 (1.9)	1 (1.9)	0	2 (3.6)
Osteoarthritis	0	0	0	1 (1.8)
Pain in extremity	1 (1.9)	2 (3.7)	0	0
Rheumatoid arthritis	1 (1.9)	0	0	1 (1.8)
Nervous system disorders	4 (7.4)	2 (3.7)	2 (3.6)	4 (7.3)
Dizziness	0	1 (1.9)	0	0
Headache	4 (7.4)	1 (1.9)	1 (1.8)	3 (5.5)
Hypersomnia	0	0	0	1 (1.8)
Lethargy	0	0	0	1 (1.8)
Nerve compression	0	0	1 (1.8)	0
Paraesthesia	0	0	0	1 (1.8)

Table 15. Number (%) of Subjects Who Reported Treatment-Emergent Adverse Events (Safety Population)

System Organ Class[a] Preferred Term	Treatment			
	PPM-204 60 mg N=54	PPM-204 30 mg N=54	Pioglitazone N=55	Placebo/Pioglitazone N=55
Psychiatric disorders	1 (1.9)	3 (5.6)	0	0
Insomnia	1 (1.9)	2 (3.7)	0	0
Stress	0	1 (1.9)	0	0
Renal and urinary disorders	1 (1.9)	1 (1.9)	1 (1.8)	0
Haematuria	1 (1.9)	1 (1.9)	1 (1.8)	0
Reproductive system and breast disorders	1 (1.9)	0	0	0
Breast pain	1 (1.9)	0	0	0
Respiratory, thoracic and mediastinal disorders	4 (7.4)	2 (3.7)	3 (5.5)	3 (5.5)
Asthma	0	0	1 (1.8)	0
Cough	1 (1.9)	1 (1.9)	2 (3.6)	1 (1.8)
Dyspnoea	0	1 (1.9)	0	0
Pharyngolaryngeal pain	0	0	0	1 (1.8)
Pleurisy	1 (1.9)	0	0	0
Pleuritic pain	1 (1.9)	0	0	0
Pulmonary congestion	1 (1.9)	1 (1.9)	0	0
Respiratory disorder	1 (1.9)	0	0	0
Rhinorrhoea	0	0	0	1 (1.8)
Sinus congestion	1 (1.9)	0	0	0
Skin and subcutaneous tissue disorders	4 (7.4)	2 (3.7)	1 (1.8)	3 (5.5)
Acne	0	0	0	1 (1.8)
Alopecia	1 (1.9)	0	0	0
Dermatitis contact	0	0	0	1 (1.8)
Ingrowing nail	1 (1.9)	0	0	0
Pain of skin	0	0	1 (1.8)	0
Rash	1 (1.9)	2 (3.7)	0	0
Seborrhoeic dermatitis	0	0	0	1 (1.8)
Skin fissures	1 (1.9)	0	0	0
Vascular disorders	0	1 (1.9)	0	1 (1.8)
Hypertension	0	1 (1.9)	0	1 (1.8)

Non SAE/SAE results are not separated out.
MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.
Classifications of adverse events are based on the MedDRA)

a. Totals at a higher level are not necessarily the sum of those at the lower levels since a subject may have reported ≥2different adverse events within the higher level category.

Treatment-Related Adverse Events: A summary of the number of subjects reporting TEAEs by drug relationship is provided in Table 16.

Table 16. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events by Drug Relationship

System Organ Class[a] Preferred Term	Treatment			
	PPM-204 60 mg N=54	PPM-204 30 mg N=54	Pioglitazone N=55	Placebo/Pioglitazone N=55
Any adverse event	5 (9.3)	5 (9.3)	8 (14.5)	3 (5.5)
Eye disorders	0	0	2 (3.6)	0
Eyelid oedema	0	0	1 (1.8)	0
Vision blurred	0	0	1 (1.8)	0
Gastrointestinal disorders	0	2 (3.7)	1 (1.8)	2 (3.6)
Abdominal pain	0	0	0	1 (1.8)
Constipation	0	1 (1.9)	0	0
Flatulence	0	0	1 (1.8)	0
Nausea	0	0	0	1 (1.8)
Stomach discomfort	0	1 (1.9)	0	0
General disorders and administration site conditions	2 (3.7)	1 (1.9)	2 (3.6)	0
Asthenia	0	1 (1.9)	0	0
Chest pain	1 (1.9)	0	0	0
Oedema	1 (1.9)	0	0	0
Oedema peripheral	0	0	1 (1.8)	1 (1.8)
Investigations	2 (3.7)	2 (3.7)	2 (3.6)	1 (1.8)
Blood creatinine increased	1 (1.9)	0	1 (1.8)	0
Cardiac murmur	0	1 (1.9)	0	0
Electrocardiogram QT prolonged	0	0	0	1 (1.8)
Weight decreased	1 (1.9)	0	0	0
Weight increased	0	1 (1.9)	1 (1.8)	0
Metabolism and nutrition disorders	0	1 (1.9)	0	0
Anorexia	0	1 (1.9)	0	0
Nervous system disorders	0	1 (1.9)	0	0
Dizziness	0	1 (1.9)	0	0
Renal and urinary disorders	0	0	1 (1.8)	0
Haematuria	0	0	1 (1.8)	0
Respiratory, thoracic and mediastinal disorders	1 (1.9)	0	0	0
Respiratory disorder	1 (1.9)	0	0	0
Skin and subcutaneous tissue disorders	1 (1.9)	0	0	0
Alopecia	1 (1.9)	0	0	0

Classifications of adverse events are based on the MedDRA.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.
a. Totals at a higher level are not necessarily the sum of those at the lower levels since a subject may have reported ≥2 different adverse events within the higher level category.

Serious Adverse Events (SAEs): Two (2) subjects had SAEs (Table 17). No SAEs were considered related to test article.

Table 17. Number (%) of Subjects Reporting Serious Adverse Events

System Organ Class[a] Preferred Term	Treatment			
	PPM-204 60 mg N=54	PPM-204 30 mg N=54	Pioglitazone N=55	Placebo/Pioglitazone N=55
Any adverse event	1 (1.9)	0	1 (1.8)	0
Cardiac disorders	1 (1.9)	0	0	0
Myocardial infarction	1 (1.9)	0	0	0
Pericarditis	1 (1.9)	0	0	0
Infections and infestations	0	0	1 (1.8)	0
Gastroenteritis	0	0	1 (1.8)	0

Classifications of adverse events are based on the MedDRA.
MedDRA = Medical Dictionary for Regulatory Activities.
a. Totals at a higher level are not necessarily the sum of those at the lower levels since a subject may have reported ≥2 different adverse events within the higher level category.

Deaths: No deaths occurred during this study.

Discontinuations due to Adverse Events: Twelve (12) subjects discontinued because of AEs (Table 18). Three (3) subjects were discontinued for hematuria, 1 in the 60-mg PPM-204 treatment group, 1 in the placebo group, and 1 in the pioglitazone group.

Table 18. Number (%) of Subjects Reporting Adverse Events Causing Withdrawal From the Study

System Organ Class[a] Preferred Term	Treatment			
	PPM-204 60 mg N=54	PPM-204 30 mg N=54	Pioglitazone N=55	Placebo/Pioglitazone N=55
Any adverse event	3 (5.6)	1 (1.9)	3 (5.5)	5 (9.1)
Blood and lymphatic system disorders	0	0	1 (1.8)	0
Anaemia	0	0	1 (1.8)	0
Cardiac disorders	1 (1.9)	0	0	0
Myocardial infarction	1 (1.9)	0	0	0
Gastrointestinal disorders	0	0	0	1 (1.8)
Abdominal pain	0	0	0	1 (1.8)
Investigations	1 (1.9)	0	1 (1.8)	2 (3.6)
Alanine aminotransferase increased	0	0	0	1 (1.8)
Blood creatinine increased	1 (1.9)	0	1 (1.8)	1 (1.8)
Metabolism and nutrition disorders	0	0	0	1 (1.8)
Hyperglycaemia	0	0	0	1 (1.8)
Nervous system disorders	0	1 (1.9)	0	0
Headache	0	1 (1.9)	0	0
Renal and urinary disorders	1 (1.9)	0	1 (1.8)	1 (1.8)
Haematuria	1 (1.9)	0	1 (1.8)	1 (1.8)

AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities.
Classifications of AEs are based on the MedDRA.
a. Totals at a higher level are not necessarily the sum of those at the lower levels since a subject may have reported ≥2 different AEs within the higher level category.

CONCLUSION: Thirty (30) mg pioglitazone showed a significant decrease of FPG after 12 weeks of treatment; the magnitude of the effect increased at later time points. The decrease of HbA1c at 24 weeks was consistent with the changes in FPG and in adiponectin. PPM-204 showed a modest dose-dependent hypoglycemic effect: the observed improvement in FPG at 12 weeks with the 60-mg dose was smaller than with pioglitazone 30 mg and met predefined

futility criteria for study termination. PPM-204 did not have a significant effect on HbA1c at 12 and 24 weeks.

All treatments were well tolerated, but there were trends in favor of PPM-204 for body weight and incidence of edema. PPM-204 (30 and 60 mg) did not have a significant effect on body weight at 12 and 24 weeks; treatment with PPM-204 did not increase the incidence of edema above that of placebo. The incidence of edema for pioglitazone at 12 weeks was 13% versus 4% for 30 mg PPM-204 and 0% for 60 mg PPM-204. Pioglitazone (30 mg) also produced a significant weight increase: the weight gain increased in proportion to the duration of treatment.