CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-024

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-024	Submission Date: 3/31/06
Brand Name	ACTOPLUS MET XR
Generic Name	Pioglitazone Hydrochloride and Metformin Hydrochloride Extended Release Tablets
Reviewer	Jayabharathi Vaidyanathan, Ph.D.
Team Leader (Acting)	Jim Wei, Ph.D.
OCP Division	DCP-2
OND Division	Division of Metabolic and Endocrine Products
Sponsor	Takeda
Submission Type	505 (b) (2)
Formulation; Strength(s)	15 mg/ 1000 mg and 30 mg/ 1000 mg ; Oral tablets
Indication	Treatment of Type 2 Diabetes Mellitus

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I Executive Summary

Takeda has developed a fixed-dose combination tablet formulated as 15 mg/1000 mg and 30 mg/1000 mg strengths from the following active ingredients from approved compounds Actos (pioglitazone HCl) NDA 21-073 held by Takeda Pharmaceuticals and Fortamet (metformin HCl extended release) NDA 21-574 held by Andrx Labs respectively.

The efficacy and safety of the concomitant use of pioglitazone and metformin has previously been evaluated in controlled clinical trials (NDA 21-073). Concomitant administration of the separate commercial pioglitazone and metformin tablets in adult patients with type 2 diabetes was approved by the FDA in 1999 as a part of the original marketing approval of pioglitazone.

Pioglitazone is approved for once-daily administration at doses of 15, 30 and 45 mg. Metformin extended release (Fortamet) is available in 500, and 1000 mg tablets and is approved for individualized treatment up to a maximum daily dose of 2500 mg in adults depending on effectiveness and tolerability. To improve gastrointestinal tolerability, it is recommended that Fortamet be administered with an evening meal. Fortamet has been shown to be bioequivalent to immediate release metformin under these dosing conditions. Pioglitazone can be administered regardless of meals.

To aid in the approval of this application the sponsor has submitted 2 bioequivalence studies and 1 food effect study. There were no clinical studies done with the to-be marketed combination product and the pharmacokinetic studies were designed to bridge the proposed combination tablets to the clinical safety and efficacy database supporting the use of pioglitazone in combination with metformin existing under the approved NDA.

A Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed the information provided in the NDA 22-024 for ACTOPLUS MET XR tablets and finds it acceptable. Recommendations and labeling comments should be sent to the sponsor as appropriate.

_____

Jaya Vaidyanathan, Ph.D.
OCP/DCP-2

A clinical pharmacology briefing was held for NDA 22-024 on December 18, 2006; the attendees were Dr. Chandra Sahajwalla, Dr. Suresh Doddapaneni, Dr. Emmanuel Fadiran, Dr. Jim Wei, Dr. Robert Misbin, Dr. Jayabharathi Vaidyanathan and Carol Noory.

B Phase 4 Commitments

None.

C Summary of CPB Findings

The summary of results from the clinical pharmacology studies is provided below.

Bioequivalence:

Bioequivalence studies were conducted for the two strengths of combination tablet. Results indicate that the pioglitazone and metformin from ACTOPLUS MET XR 15 mg/1000 mg and 30 mg/1000 mg tablets were bioequivalent to Actos and Fortamet commercial tablets given concomitantly under fed conditions. The conclusions are based on the findings that the 90% CI for the ratio of geometric means (test/reference) for AUC and C_{max} were within the 80-125% interval.

Food effect:

The results demonstrated that after administration of the highest strength combination tablet (30 mg/1000 mg) under fed conditions, the AUC of pioglitazone was similar as compared to the fasted state while there was a decrease in Cmax by approximately 18%. While the metformin AUCinf and Cmax increased by 85% and 98% respectively in presence of food. Since metformin is indicated to be administered with food, ACTOPLUS MET XR is also recommended to be administered with food.

II QBR

A General Attributes

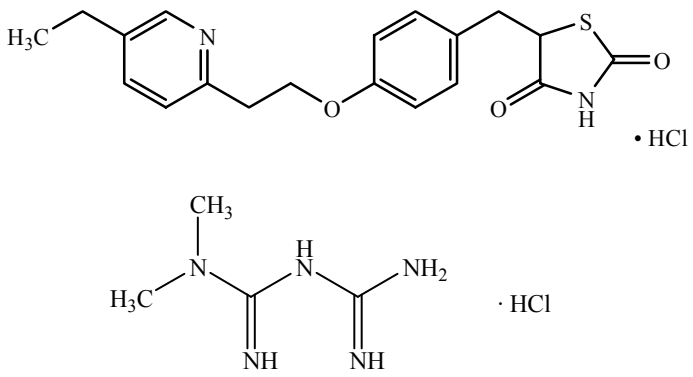
What are the highlights of the chemistry and physico-chemical properties of ACTOPLUS MET XR?

ACTOPLUS MET XR contains 2 oral antihyperglycemic drugs used in type 2 diabetes; pioglitazone hydrochloride and metformin hydrochloride. Pioglitazone ([(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride) (Figure 1) belongs to thiazolidinedione class. The molecule contains one asymmetric center, and the synthetic compound is a racemate. The two enantiomers of pioglitazone interconvert *in vivo*. Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S$•HCl and a molecular weight of 392.90.

Metformin hydrochloride (N, N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other class of oral antihyperglycemic

agents. It is a white crystalline powder with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.62.

Figure 1: Chemical structure of pioglitazone (top) and metformin (bottom).



What is the proposed mechanism (s) of action and therapeutic indication?

ACTOPLUS MET XR combines two antihyperglycemic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes: pioglitazone hydrochloride, a member of thiazolidinedione class, and metformin, a member of the biguanide class. This is a 505 (b) (2) application. The proposed indication for the combination tablet is the same as that for the individual drugs.

Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

Metformin improves glucose tolerance in patients with type 2 diabetes, reducing both basal and postprandial plasma glucose levels. Metformin also decreases hepatic glucose production, decreases intestinal absorption of glucose and improves sensitivity by increasing peripheral glucose uptake and utilization.

The proposed indication for ACTOPLUS MET XR is as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a combination of pioglitazone and metformin or whose diabetes is not adequately controlled with metformin alone, or for those patients who have initially responded to pioglitazone alone and require additional glycemic control.

What is the proposed dose and dosage form?

ACTOPLUS MET XR is available in 15 mg pioglitazone hydrochloride (as the base)/1000 mg metformin hydrochloride extended-release and 30 mg pioglitazone hydrochloride (as the base)/1000 mg metformin hydrochloride extended-release tablets.

ACTOPLUS MET XR is proposed be given once daily with the evening meal to reduce the gastrointestinal side effects associated with metformin.

Starting dose for patients inadequately controlled on metformin monotherapy
Based on the usual starting dose of pioglitazone (15-30 mg daily), ACTOPLUS MET XR is proposed to be initiated at either the 15 mg/1000 mg or 30 mg/1000 mg tablet strength once daily, and titrated after assessing adequacy of therapeutic response.

Starting dose for patients who initially responded to pioglitazone monotherapy and require additional glycemic control
Based on the usual starting doses of metformin (850 to 1000 mg total daily dose), ACTOPLUS MET XR is proposed to be initiated at either the 15 mg/1000 mg once daily or 30 mg/1000 mg tablet strength once daily, and titrated after assessing adequacy of therapeutic response.

Starting dose for patients switching from combination therapy of pioglitazone plus metformin as separate tablets
ACTOPLUS MET XR is proposed to be initiated with either the 15 mg/1000 mg or 30 mg/1000 mg tablet strengths based on the dose of pioglitazone and metformin already being taken.

B General Clinical Pharmacology

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

No clinical studies with the drug product were performed in support of this submission. Consistent with the requirements for a 505 (b) (2) application, the clinical pharmacology studies were performed to demonstrate the bioequivalence of the combined drug product to the commercially available reference products. Two doses of the pioglitazone/metformin extended release fixed dose tablet (15 mg/1000 mg and 30 mg/1000 mg) were evaluated in 2 bioequivalence studies; the highest dose was evaluated in a food-effect study.

Does this combination drug prolong QT or QTc interval?

The sponsor has not submitted any study determining the effect of Actoplus Met XR on cardiac repolarization. However, both Actos® (pioglitazone) and Fortamet® (metformin

extended release) are approved drugs in the US and no reports of any adverse effects of these drugs due to their effect on cardiac repolarization has been reported thus far.

C Intrinsic Factors

The effects of various intrinsic factors (e.g., hepatic, renal, gender, elderly) were provided in the original NDA for each drug.

D Extrinsic Factors

Is there any drug-drug interaction between pioglitazone and metformin?

Specific pharmacokinetic drug interaction studies with ACTOPLUS MET XR have not been performed, although such studies have been conducted with the individual pioglitazone and metformin components. The proposed label has the following statement: "Co-administration of a single dose of immediate-release metformin (1000 mg) and pioglitazone after 7 days of pioglitazone (45 mg) did not alter the pharmacokinetics of the single dose of metformin."

E General Biopharmaceutics

What is the formulation of ACTOSPLUS MET XR tablets?

ACTOPLUS MET XR tablets are a combination product containing either 15 mg + 1000 mg or 30 mg + 1000 mg of pioglitazone hydrochloride (as the free base) and metformin extended release respectively. The composition of the tablets used in clinical pharmacology studies are shown in Table 1. The proposed tablets are white, round tablets that consist of a metformin extended-release core coated with an immediate-release pioglitazone layer. The 2 tablet strengths differ only in tablet weight. The tablets used in clinical pharmacology studies are identical in composition to those intended for commercial distribution except for the addition of imprinting with unique markings, utilizing different color inks for each of the tablet strength.

Table 1: Composition of Actoplus Met XR tablets

Table 1.a Composition of AD-4833XT Tablets (Formulation 2)

Components (mg/tablet)	Function	15/1000 mg	30/1000 mg
(b) (4) **Extended-Release Core**			
(b) (4)	Active ingredient	(b) (4)	
Sodium lauryl sulfate, NF		(b) (4)	
Povidone (b) (4) USP			
Magnesium stearate, NF			
(b) (4)			
Cellulose acetate, NF			
Triacetin, USP			
PEG 400, NF			
(b) (4) **Layer**			
(b) (4)	Active ingredient	(b) (4)	
(b) (4)		(b) (4)	
HPC, NF			
Lactose monohydrate, NF			
Titanium dioxide, USP			
Polyethylene glycol 8000, NF			
HPC, NF			
PEG 8000, NF			
Titanium dioxide, USP			
Candelilla wax powder, NF			
(b) (4)			
(b) (4)			
Total Weight (mg)		1254.52	1291.22

Source: Module 3, Section 3.2.P.1.
BP=British Pharmacopeia, NF=National Formulary, USP=United States Pharmacopeia, PEG=polyethylene glycol, HPC=hydroxypropyl cellulose, qs=quantity sufficient.
Tablets used in clinical studies were manufactured by Andrx Pharmaceuticals Inc., Fort Lauderdale, Florida. The lot numbers for the tablets used in the pivotal bioequivalence and food-effect studies were as follows: Lot Number 578R023A (15/1000 mg tablet) and Lot Numbers 573R023A and 573R023B (30/1000 mg tablet).
(a) Equivalent to 15 mg pioglitazone free base.
(b) Equivalent to 30 mg pioglitazone free base.
(c) Removed during processing.

The metformin extended-release component of the ACTOPLU MET XR is an extended release formulation of metformin for once-daily administration, which is based on the proprietary SCOT (single composition osmotic tablet) technology of Andrx Pharmaceuticals. This consists of an active core encased in a rate controlling semi-permeable membrane with 2 laser-drilled exit orifices. The rate of metformin release from the tablet is controlled by the osmotic gradient and the characteristics of the semi-permeable membrane. (b) (4) Pioglitazone is coated on the surface of metformin core using (b) (4)

Is the dissolution method appropriate for ACTOPLUS MET XR tablets?

Dissolution will be reviewed by Chemistry Reviewer. Please refer to CMC review for details.

Bioequivalence Study:

1) Is the combination tablet formulation of pioglitazone and metformin (15 mg/1000 mg) bioequivalent to concomitant dosing of pioglitazone 15 mg and metformin extended release 1000 mg (15 mg + 1000 mg) commercial tablets in healthy subjects?

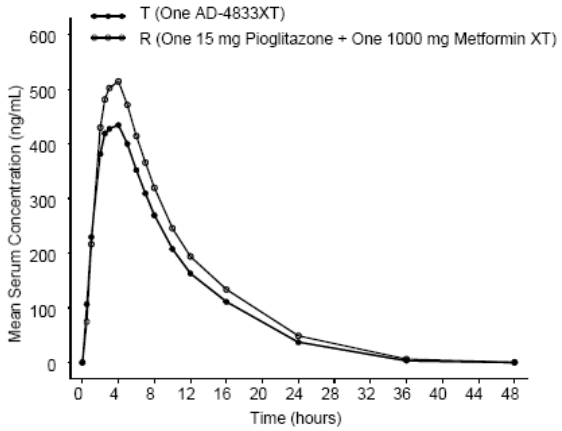
Yes. Both pioglitazone and metformin components from the fixed dose combination tablet were bioequivalent to the individual commercial tablets (1 pioglitazone 15 mg + 1 metformin XT 1000 mg).

An open-label, randomized, 2-sequence, 2-period crossover BE study was conducted in healthy subjects (64 enrolled; 60 completed; 18-55 yrs) in the fed state (Study OPIXT002). The study drug was administered 30 minutes following a high fat evening meal. A washout interval of 7 days separated the 2 treatments. Blood samples were collected for pioglitazone and metformin PK analysis through 48 h following each treatment. The treatments were:

Treatment	Drug	Dose	Form
Test Drug	AD-4833XT	Pioglitazone 15 mg/ metformin XT 1000 mg	Fixed-dose combination product
Reference Drug	Pioglitazone Metformin XT	15 mg 1000 mg	Commercial tablets

The mean serum concentrations for pioglitazone from the two treatments are shown in Figure 2.

Figure 2: Mean serum pioglitazone concentration-time profile following administration of the combination tablet and separate commercial tablets



Mean serum concentrations of pioglitazone were lower after dosing with the test treatment (Fixed dose combination tablet) than after dosing with the reference treatment (Actos 15 mg + Fortamet 1000 mg). By 48 h, pioglitazone levels were below the limit of quantification following both treatments.

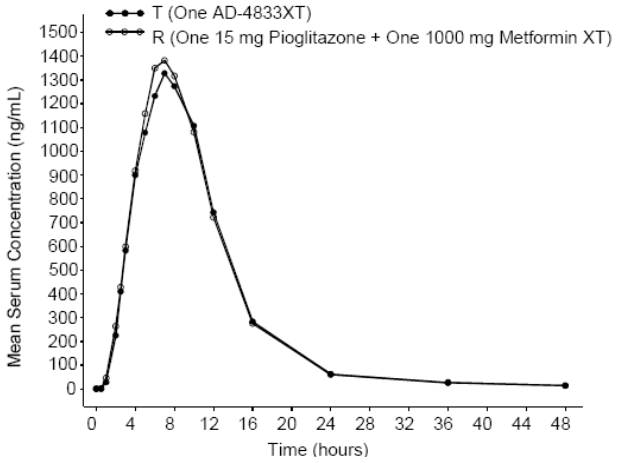
Statistical analysis of the PK parameters indicated that the 90% CI for the ratios of the LS means for AUClast, AUCinf, and Cmax of pioglitazone were well within the prespecified 80-125% bounds and therefore met the criteria of bioequivalence (Table 1). The Tmax was also similar between the two treatments (~3 h).

Table 2: Statistical summary of pioglitazone following administration of combination tablet (Test) and separate commercial tablets (Reference)

Parameter (units) (a)	n	Treatment	LS Mean (b)	LS Mean Ratio of T/R (90% CI) (%)
AUC(0-inf) (ng·hr/mL)	59	T R	4888.044 5749.983	85.01 (81.59, 88.58)
AUC(0-tlqc) (ng·hr/mL)	60	T R	4474.271 5287.544	84.62 (80.79, 88.63)
Cmax (ng/mL)	60	T R	471.61 545.36	86.48 (82.26, 90.91)
Tmax (hr) (c)	60	T R	3.000 3.000	N/A
λz (1/hr) (c)	60	T R	0.12552 0.11870	N/A

The mean serum metformin concentrations are shown in Figure 3 below. Following both treatments, the serum metformin concentrations were identical. By 48 h post-dose the serum levels were near the lower limit of quantitation (10 ng/ml).

Figure 3: Mean serum metformin concentration-time profile following administration of the combination tablet and separate commercial tablets



The PK parameters of metformin following the two treatments were also similar. The median Tmax for metformin was 7 h for both treatments. The statistical analysis indicated that the 90% CI for the ratios of LS means for AUClast, AUCinf, and Cmax of metformin were within the 80-125% interval for establishing the bioequivalence (Table 3).

Table 3: Statistical summary of metformin following administration of combination tablet (Test) and separate commercial tablets (Reference)

Parameter (units) (a)	n	Treatment	LS Mean (b)	LS Mean Ratio of T/R (90% CI) (%)
AUC(0-inf) (ng·hr/mL)	50	T R	14061.172 14505.307	96.94 (93.62, 100.38)
AUC(0-tlqc) (ng·hr/mL)	60	T R	13875.394 14275.745	97.20 (94.25, 100.24)
Cmax (ng/mL)	60	T R	1504.31 1550.17	97.04 (93.29, 100.94)
Tmax (hr) (c)	60	T R	7.000 7.000	N/A
λz (1/hr) (c)	50	T R	0.07605 0.07538	N/A

Note: The sponsor conducted analysis after removal of subjects 36, 57 102, and 69. Subjects 36 and 57 discontinued after period 1 due to adverse events following test administration, while subjects 102 and 69 were withdrawn because of protocol violations of positive urine drug screen after reference treatment. Analysis including these subjects was conducted by the reviewer and resulted in comparable results to that presented in tables above (Table 4).

Table 4: Statistical analysis of PK parameter data from all subjects enrolled

PK Parameter	Pioglitazone			Metformin		
	LS Mean Reference	LS Mean Test	Ratio (90%CI)	LS Mean Reference	LS Mean Test	Ratio (90%CI)
AUClast	5320.73	4495.68	84.49 (80.68 – 88.49)	14305.44	13898.80	97.16 (94.22 – 100.19)
AUCinf	5774.43	4886.48	84.62 (81.25 – 88.14)	14669.12	14243.18	97.10 (94.20 – 100.08)
Cmax	546.18	471.61	85.79 (81.62 – 90.17)	1565.73	1520.50	97.11 (b) (4)

2) Is the combination tablet formulation of pioglitazone and metformin extended release (30 mg/1000 mg) bioequivalent to concomitant dosing of pioglitazone 30 mg and metformin extended release 1000 mg (30 mg + 1000 mg) commercial tablets in healthy subjects?

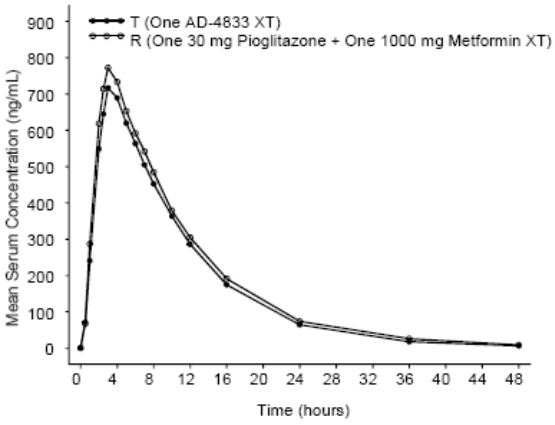
Yes. Both pioglitazone and metformin components from the fixed dose combination tablet were bioequivalent to the individual commercial tablets (1 pioglitazone 30 mg + 1 metformin XT 1000 mg).

In order to address the bioequivalence of the 30 mg/1000 mg combination tablet, an open-label, randomized, 2-period crossover study (Study OPIXT003) was conducted in healthy subjects under fed conditions. As in the previous BE study the study drug was administered 30 minutes following a high fat evening meal. A washout interval of 7 days separated the 2 treatments. Blood samples were collected for pioglitazone and metformin PK analysis through 48 h following each treatment. The two treatments were:

Treatment	Drug	Dose	Form
Test	AD-4833XT	Pioglitazone 30 mg/ metformin XT 1000 mg	Fixed-dose combination product
Reference	Pioglitazone Metformin XT	30 mg 1000 mg	Commercial tablets

Results indicate that the serum pioglitazone concentrations were similar after dosing with both the test and reference treatments (Figure 4). By 48 h post dose mean pioglitazone concentrations were near or below the limit of quantification.

Figure 4: Mean serum concentration-time profile for pioglitazone following administration of combination tablet (test) and separate commercial tablets (reference)



Statistical analysis of the PK parameters indicated that the 90% CI for the ratios of the LS means for AUCinf, AUClast and Cmax of pioglitazone were within the 80-125% interval and therefore met the criteria for bioequivalence (Table 5). The median Tmax was similar for each treatment.

Table 5: Statistical analysis of pharmacokinetic parameters for pioglitazone

Parameter (units) (a)	n	Treatment	LS Mean (b)	LS Mean Ratio of T/R (90% CI) (%)
AUC(0-inf) (ng·hr/mL)	55	T R	7936.372 8929.429	88.88 (84.97, 92.97)
AUC(0-tlqc) (ng·hr/mL)	57	T R	7503.776 8464.867	88.65 (84.72, 92.75)
Cmax (ng/mL)	57	T R	743.67 832.65	89.31 (83.97, 95.00)
Tmax (hr) (c)	57	T R	3.00 3.00	N/A
λz (1/hr) (c)	55	T R	0.12013 0.10808	N/A

Similarly, serum metformin concentrations were similar after administration of the combination tablet and the reference treatment (1 pioglitazone 30 mg + 1 metformin XT 1000 mg commercial tablets). By 48 h post dose concentrations were below the limit of quantification. The statistical analysis of the PK parameters for metformin also indicated bioequivalence between the two treatments (Figure 5 & Table 6). The median Tmax for metformin was longer following the reference treatment.

Figure 5: Mean serum metformin concentrations over time

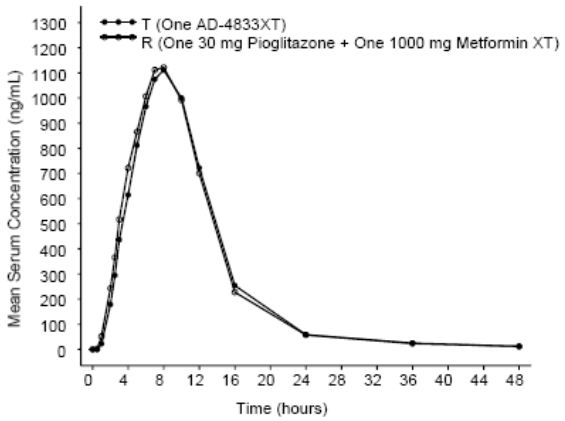


Table 6: Statistical analysis of PK parameters for metformin

Parameter (units) (a)	n	Treatment	LS Mean (b)	LS Mean Ratio of T/R (90% CI) (%)
AUC(0-inf) (ng·hr/mL)	54	T R	12256.946 12266.902	99.92 (95.18, 104.89)
AUC(0-tlqc) (ng·hr/mL)	58	T R	11933.460 11892.614	100.34 (95.72, 105.19)
Cmax (ng/mL)	58	T R	1284.54 1280.23	100.34 (96.42, 104.42)
Tmax (hr) (c)	58	T R	8.000 7.008	N/A
λz (1/hr) (c)	54	T R	0.07839 0.07827	N/A

Note: The sponsor used data from subjects who finished both treatments. Subjects 12 and 16 received the reference treatment in period 1 and voluntarily withdrew consent and discontinued in the study; Subject 50 received both treatments, then voluntarily withdrew consent and discontinued in period 2; Subject 5 received reference treatment in period 1, but was withdrawn due to protocol violation (positive urine drug result). In addition sponsor mentioned that subject 20's serum concentration from reference pioglitazone treatment were all below the limit of quantification, therefore this subject was excluded from pioglitazone analysis. Analysis including these subjects was conducted by the reviewer and resulted in comparable results to that presented in tables above (Table 7).

Table 7: Statistical analysis of PK parameter data from all subjects enrolled

PK Parameter	Pioglitazone			Metformin		
	LS Mean Reference	LS Mean Test	Ratio (90%CI)	LS Mean Reference	LS Mean Test	Ratio (90%CI)
AUClast	8519.01	7537.82	88.48 (84.61 – 92.53)	12004.49	12012.95	100.07 (95.49 – 104.87)
AUCinf	8996.35	7988.61	88.80 (85.01 – 92.75)	12311.58	12319.75	100.07 (95.67 – 104.67)
Cmax	836.36	740.52	88.54 (83.30 –94.11)	1290.19	1292.29	100.16 (96.27 – 104.21)

What is the effect of food on the bioavailability of Actoplus Met XR?

Food decreased the Cmax of pioglitazone from the combination tablet by 18% with no change in exposure. On the other hand in presence of food, there is about 85% - 100% increase in AUC and Cmax of metformin component from the combination tablet.

In order to determine the effect of food on the absorption of pioglitazone and metformin from the combination tablet, an open-label, randomized, single-dose, 2-period, crossover design study was conducted. Subjects were randomly assigned to 1 of 2 sequences (12 subjects per sequence) and received the fixed dose combination tablet (30 mg/1000 mg) in fasting state or after a high fat meal. There was a washout period of 7 days between treatments.

The mean serum pioglitazone concentrations over time are shown in the Figure 6 below. Under fasting conditions, pioglitazone from the combination tablet was rapidly absorbed as compared to under fed conditions. Statistical comparisons of the PK parameters are presented in Table 8. For pioglitazone, the 90% CI of the fed/fasted LS mean ratios for AUClast, AUCinf were within the 80-125% interval indicating that the total exposure was not altered with food. However the Cmax decreased 18% in presence of food and this was statistically significant with the 90% CI being lower than the 80-125% range. Tmax increased by 3 h in presence of food.

Figure 6: Mean serum pioglitazone concentrations over time

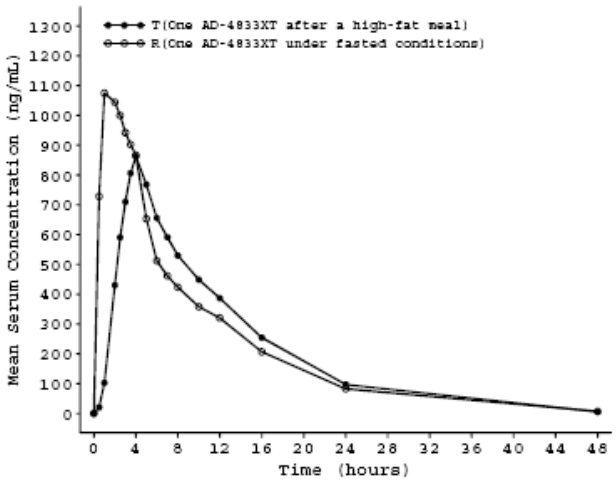
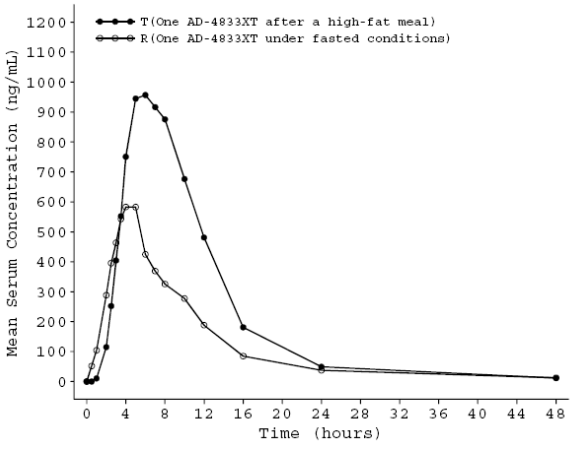


Table 8: Statistical comparisons of pioglitazone from combination tablet (30 mg/1000 mg) administered in presence (T) and absence (R) of food.

Parameter (units) (a)	n	Treatment	LS Mean (b)	LS Mean Ratio of T/R (90% CI) (%)
AUC(0-inf) (ng·hr/mL)	24	T R	9452.170 9902.787	95.45 (82.74, 110.11)
AUC(0-tlqc) ng·hr/mL)	24	T R	8695.991 9261.217	93.90 (80.24, 109.87)
Cmax (ng/mL)	24	T R	880.54 1078.95	81.61 (70.63, 94.30)
Tmax (hr) (c)	24	T R	4.000 1.008	N/A
λz (1/hr) (c)	24	T R	0.11365 0.11287	N/A

The mean serum metformin concentrations time profile is shown in Figure 7. As seen there is a delay in Tmax in presence of food, however food increases the exposure to metformin.

Figure 7: Mean serum metformin concentrations over time



The statistical comparisons of the PK parameters are shown in Table 9. In presence of food there is approximately 85%, 100%, and 98% increases in AUCinf, AUClast and Cmax of the Actoplus met XR tablet. The 90% CI for the LS mean ratios for these PK parameters were all above the 80-125% range indicating that the peak and total exposure of metformin is increased when the combination tablet is administered with food.

Table 9: Statistical comparisons of metformin from combination tablet (30 mg/1000 mg) administered in presence (T) and absence (R) of food.

Parameter (units) (a)	n	Treatment	LS Mean (b)	LS Mean Ratio of T/R (90% CI) (%)
AUC(0-inf) (ng·hr/mL)	21	T R	9776.216 5293.188	184.69 (155.23, 219.75)
AUC(0-tlqc) (ng·hr/mL)	24	T R	9832.542 4903.882	200.51 (170.01, 236.47)
Cmax (ng/mL)	24	T R	1117.94 565.13	197.82 (160.30, 244.12)
Tmax (hr) (c)	24	T R	6.000 4.008	N/A
λz (1/hr) (c)	22	T R	0.13513 0.09899	N/A

Comment: The effect of food observed in this study on pioglitazone and metformin XR is similar to that observed for the individual components based on the package insert of Actos and Fortamet respectively. The delay in Tmax and decrease in Cmax for pioglitazone will most likely not have an impact on efficacy of pioglitazone since there was no change in exposure in presence of food. Metformin is indicated to be administered in presence of food to decrease the GI adverse events. The AUC and Cmax values obtained in presence of food in this study is similar to that (metformin component of reference and test product) seen in BE study OPIXT003 done under fed conditions. Therefore this suggests that absorption of metformin from the formulation is decreased in fasting state. The sponsor has proposed that the Actoplus met XR tablet be taken with an evening meal which is acceptable.

F Analytical

Have the analytical methods been sufficiently validated?

Yes.

An LC/MS/MS method for the quantification of pioglitazone in human serum was used. The internal standard for pioglitazone used was an analog (b) (4). The analyte and internal standard were extracted from human serum using solid-phase extraction. The residue was reconstituted using mobile phase and injected onto an LC/MS/MS. The LLOQ was 25.0 ng/ml and the standard curve was linear up to 2500 ng/ml. Intra-assay and inter-assay precision were determined from the relative standard deviations of the quality control samples. The values were all below 6% (Table 10). The accuracy was

determined by comparing the mean measured concentrations of the quality control sample with their nominal concentrations (Table 10).

Table 10: Intra-assay and inter-assay precision and accuracy for pioglitazone in serum

Nominal Concentration	2000	1000	75.0	2000	1000	75.0	2000	1000	74.9
Average Concentration	2215	987	74.3	2207	1030	73.6	2166	977	74.0
Standard Deviation	63.6	40.0	2.45	56.8	18.3	0.881	112	30.0	1.30
Precision (%)	2.9%	4.1%	3.3%	2.6%	1.8%	1.2%	5.2%	3.1%	1.8%
Accuracy (%)	110.8%	98.7%	99.1%	110.3%	103.0%	98.1%	108.3%	97.7%	98.8%
N	6	6	6	6	6	6	6	6	6

An LC/MS/MS method was used for analysis of metformin in human serum. The internal standard used for metformin was (b) (4). The analyte and internal standard were extracted using human serum using protein precipitation. The LLOQ was 10.0 ng/ml and the standard curve was linear up to 3500 ng/ml. The values of assay precision and accuracy are shown in Table 11.

Table 11: Intra-assay and inter-assay precision and accuracy for metfomin in serum

Concentration	QL 10.0 10.0 ng/mL	QC 30.0 30.0 ng/mL	QC 800 800 ng/mL	QC 3000 3000 ng/mL
Mean	9.15	29.5	792	3000
S.D.	0.627	1.96	21.1	227
%CV	6.9	6.6	2.7	7.6
%Theoretical	91.5	98.3	99.0	100.0
%Bias	-8.5	-1.7	-1.0	0.0
n	24	26	26	26

III Labeling Recommendations

(b) (4)

(b) (4)

(b) (4)

IV Appendix

A Proposed Package Insert

(b) (4)

32 pp withheld immediately after this page as (b)(4) draft labeling.

Bottles of 30	NDC 64764-310-30
Bottles of 60	NDC 64764-310-60
Bottles of 90	NDC 64764-310-90

STORAGE
ACTOPLUS MET
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed, and protect from moisture and humidity.

ACTOPLUS MET XR

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Avoid excessive heat and humidity. Dispense in a tightly closed, light-resistant container.

B Individual Study Synopsis

1) Bioequivalence study

2.0 SYNOPSIS

Title of Study: An Open-Label, Randomized, 2-Period Crossover Study to Determine the Bioequivalence of 15 mg Pioglitazone and 1000 mg Metformin HCl Extended Release (XT) When Administered as a Fixed-Dose Combination Product or Concomitantly as Commercial Tablets	
Name of Sponsor: Takeda Global Research & Development Center, Inc.	
Name of Finished Product: AD-4833XT (pioglitazone hydrochloride 15 mg/metformin hydrochloride XT 1000 mg fixed-dose combination product)	
Investigator: (b) (4)	**Study Center:** (b) (4)
Publications Based on the Study: None	
Study Period: 27 April 2005 to 6 May 2005	**Phase of Development:** Phase 1
OBJECTIVES **Primary:** The primary objective of this study was to determine the bioequivalence of a single oral dose of AD-4833XT relative to concomitant administration of the commercial pioglitazone and metformin XT tablets. **Secondary:** The secondary objective of this study was to evaluate the safety of AD-4833XT and the concomitant administration of the commercial pioglitazone and metformin XT tablets.	
METHODS This was a phase 1, open-label, randomized, 2-sequence, 2-period crossover, bioequivalence study. Subjects were assigned randomly to 1 of 2 sequences, and received a single oral dose of test treatment (1 AD-4833XT tablet) and a single oral dose of reference treatment (1 pioglitazone 15 mg commercial tablet and 1 metformin XT 1000 mg commercial tablet) in the fed state. A washout interval of 7 days separated the 2 treatments. Blood samples for the measurement of pioglitazone and metformin concentrations were collected at specified times up to 48 hours after each treatment.	

Title of Study:

An Open-Label, Randomized, 2-Period Crossover Study to Determine the Bioequivalence of 15 mg Pioglitazone and 1000 mg Metformin HCl Extended Release (XT) When Administered as a Fixed-Dose Combination Product or Concomitantly as Commercial Tablets

Pretreatment			Treatment				Final Visit
Screening	Baseline	Randomization	Period 1 (a)		Period 2 (a)		
Days -28 to -2	Day 1			Day 2 to 7	Day 1	Day 2 to 3	Day 3
			T n=32	Washout	R		
			R n=32		T		

T=Test treatment (1 AD-4833XT tablet).
R=Reference treatment (1 pioglitazone 15 mg commercial tablet and 1 metformin XT 1000 mg commercial tablet).
(a) Subjects were admitted to the clinic and dosed on Day 1 of each Period, and were discharged from the clinic on Day 3 of each Period.

Number of Subjects (Planned and Analyzed):

Planned: 64 subjects; 32 subjects per sequence

Analyzed: Pharmacokinetics—60 subjects; Safety—64 subjects.

Diagnosis and Main Criteria for Inclusion:

To qualify for study participation, subjects must have been healthy male subjects or healthy nonpregnant, nonlactating female subjects aged 18 to 55 years, inclusive; been willing to sign the informed consent form; had clinical laboratory results within the reference ranges or that were acceptable to the investigator; weighed at least 110 pounds (50 kg) and had a body mass index ≤30 kg/m^2; and had negative hepatitis panel and human immunodeficiency virus antibody test results at Screening.

Test Product, Dose and Mode of Administration, Lot Number:

Drug	Dose	Form	Route	Lot No.
AD-4833XT	Pioglitazone hydrochloride 15 mg/ metformin hydrochloride XT 1000 mg	Fixed-dose combination tablet	Oral	578R023A

Duration of Treatment:

The duration of the study for a subject who completed both treatments was 10 days.

Reference Therapy, Dose and Mode of Administration, Lot Number:

Drug	Dose	Form	Route	Lot No.
Pioglitazone hydrochloride (ACTOS®)	15 mg	Commercial tablet	Oral	A10325
Metformin hydrochloride XT (FORTAMET™)	1000 mg	Commercial tablet	Oral	575V002A

Title of Study:

An Open-Label, Randomized, 2-Period Crossover Study to Determine the Bioequivalence of 15 mg Pioglitazone and 1000 mg Metformin HCl Extended Release (XT) When Administered as a Fixed-Dose Combination Product or Concomitantly as Commercial Tablets

Criteria for Evaluation:

Pharmacokinetic:

The area under the concentration-time curve from time 0 to time of last quantifiable concentration (AUC[0-tlqc]), area under the concentration-time curve from time 0 to infinity (AUC[0-inf]), maximum observed concentration (Cmax), time at which Cmax occurred (Tmax), terminal-phase elimination rate constant (λz), and terminal elimination half-life (T1/2) were calculated for each subject from serum concentrations of unchanged pioglitazone and metformin for each treatment using a noncompartmental approach. Actual sampling times rather than scheduled sampling times were used in the computations of pharmacokinetic parameters.

Safety:

Safety variables were adverse events, clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings.

Statistical Methods:

Pharmacokinetic Analysis:

Descriptive statistics (eg, number of subjects, mean, SD, median, minimum, and maximum) were used to summarize serum concentrations by treatment and scheduled time of sampling for pioglitazone and metformin. The pharmacokinetic parameters, AUC(0-tlqc), AUC(0-inf), Cmax, Tmax, λz, and T1/2 of pioglitazone and metformin were summarized for each treatment with the following descriptive statistics: number of subjects, mean, geometric mean [for AUC(0-tlqc), AUC(0-inf) and Cmax only], SD, SE, coefficient of variation, minimum, 25th and 75th percentiles, median, and maximum.

The AUC(0-tlqc)/AUC(0-inf) ratio was determined for each subject; if the AUC(0-tlqc) value comprised less than 80% of the AUC(0-inf) value for an individual subject, that subject's AUC(0-inf) was not included in the descriptive statistics or bioequivalence assessment. The r^2 value was also calculated for each subject; if the r^2 value for λz was less than 0.80, that subject's AUC(0-inf), λz and T1/2 values were not included in the descriptive statistics or bioequivalence assessment.

An analysis of variance with fixed effects for sequence, period, treatment, and random effect for subject nested within sequence was performed on λz and the natural logarithms of AUC(0-tlqc), AUC(0-inf), and Cmax of pioglitazone and metformin. The Wilcoxon signed-rank test was performed on Tmax.

The 90% confidence intervals (CIs) for the ratios of the least-squares (LS) mean for the test treatment (1 AD 4833XT tablet) to the LS mean for the reference treatment (1 pioglitazone 15 mg commercial tablet and 1 metformin XT 1000 mg commercial tablet) were provided for the natural logarithms of AUC(0-tlqc), AUC(0-inf), and Cmax. The test treatment was considered bioequivalent to the reference treatment if the 90% CIs for AUC(0-tlqc), AUC(0-inf), and Cmax of pioglitazone and metformin were within the 80% to 125% bioequivalence range.

Title of Study:

An Open-Label, Randomized, 2-Period Crossover Study to Determine the Bioequivalence of 15 mg Pioglitazone and 1000 mg Metformin HCl Extended Release (XT) When Administered as a Fixed-Dose Combination Product or Concomitantly as Commercial Tablets

Safety Analysis:

Safety variables (adverse events, clinical laboratory evaluations, vital sign measurements, 12-lead ECG results, and physical examination findings), and other safety assessments (medical history findings, concurrent medical conditions, medication history, and concomitant medications) were summarized with descriptive statistics, if appropriate. Abnormal laboratory values for hematology and chemistry tests, and urinalyses, were tabulated by individual subject. Vital sign measurements that met the criteria for very low or very high values were also summarized.

SUMMARY OF RESULTS

Subject Disposition:

Sixty-four subjects (mean age 27.2 years), 35 men and 29 women, were assigned randomly to treatment at 1 study site. Sixty subjects completed the study. Subjects 036 and 057 discontinued participation in the study because of the adverse events hematoma and conjunctivitis, respectively, following administration of the test treatment (1 AD-4833XT tablet). Subjects 102 and 069 were withdrawn from the study because of the protocol violations of positive urine drug screen and positive urine alcohol screen, respectively, following concomitant administration of the reference treatment (1 pioglitazone 15 mg tablet and 1metformin XT 1000 mg).

Pharmacokinetic Results:

The 90% CIs for the ratios of the LS means for AUC(0-tlqc), AUC(0-inf), and Cmax of pioglitazone and metformin were within the 80% to 125% bioequivalence range and met the criteria for bioequivalence. Therefore, the test treatment (1 AD-4833XT tablet) was bioequivalent to the reference treatment (1 pioglitazone 15 mg commercial tablet and 1 metformin XT 1000 mg commercial tablet) for pioglitazone and metformin.

Title of Study:

An Open-Label, Randomized, 2-Period Crossover Study to Determine the Bioequivalence of 15 mg Pioglitazone and 1000 mg Metformin HCl Extended Release (XT) When Administered as a Fixed-Dose Combination Product or Concomitantly as Commercial Tablets

Statistical Analysis of Pharmacokinetic Parameters for Pioglitazone and Metformin

Parameter (units) (a)	n	Treatment	LS Mean (b)	LS Mean Ratio of T/R (90% CI) (%)
Pioglitazone				
AUC(0-inf) (ng·hr/mL)	59	T R	4888.044 5749.983	85.01 (81.59, 88.58)
AUC(0-tlqc) (ng·hr/mL)	60	T R	4474.271 5287.544	84.62 (80.79, 88.63)
Cmax (ng/mL)	60	T R	471.61 545.36	86.48 (82.26, 90.91)
Tmax (hr) (c)	60	T R	3.000 3.000	N/A
λz (1/hr) (c)	60	T R	0.12552 0.11870	N/A
Metformin				
AUC(0-inf) (ng·hr/mL)	50	T R	14061.172 14505.307	96.94 (93.62, 100.38)
AUC(0-tlqc) (ng·hr/mL)	60	T R	13875.394 14275.745	97.20 (94.25, 100.24)
Cmax (ng/mL)	60	T R	1504.31 1550.17	97.04 (93.29, 100.94)
Tmax (hr) (c)	60	T R	7.000 7.000	N/A
λz (1/hr) (c)	50	T R	0.07605 0.07538	N/A

T=Test treatment (1 AD-4833XT tablet).
R=Reference treatment (1 pioglitazone 15 mg commercial tablet and 1 metformin XT 1000 mg commercial tablet).
(a) An analysis of variance with fixed effects for sequence, period, treatment, and random effect for subject nested within sequence was performed on λz and the natural logarithms of AUC(0-tlqc), AUC(0-inf), and Cmax of pioglitazone and metformin; the Wilcoxon signed rank test was performed on Tmax.
(b) Median values are presented for Tmax.
(c) Pioglitazone Tmax: P=0.599, λz: P=0.072; metformin Tmax: P=0.183, λz: P=0.900.

Safety Results:

The incidence of adverse events was similar for both treatment groups. Adverse events were reported for 14 of 62 (22.6%) subjects after administration of the test treatment (1 AD-4833XT tablet) and 12 of 62 (19.4%) subjects after administration of the reference treatment (1 pioglitazone 15 mg commercial tablet and 1 metformin XT 1000 mg commercial tablet).

Ten of 62 subjects (16.1%) experienced adverse events after administration of the test treatment (1 AD-4833XT tablet) that were considered by the investigator to be at least possibly related to study drug; these were abdominal distention, stomach discomfort, vomiting, fatigue, anorexia, back pain, and headache.

Eight of 62 subjects (12.9%) experienced adverse events after administration of the reference treatment (1 pioglitazone 15 mg commercial tablet and 1 metformin XT 1000 mg commercial tablet) that were considered by the investigator to be at least possibly related to study drug; these were nausea, vomiting, feeling cold, back pain, dizziness, and tremor. All of these events were considered mild or moderate in

Title of Study:
An Open-Label, Randomized, 2-Period Crossover Study to Determine the Bioequivalence of 15 mg Pioglitazone and 1000 mg Metformin HCl Extended Release (XT) When Administered as a Fixed-Dose Combination Product or Concomitantly as Commercial Tablets
severity, and none resulted in the discontinuation of treatment. Two subjects discontinued participation in the study because of adverse events: Subject 036 developed mild hematomas on both arms and Subject 057 experienced moderate conjunctivitis. The adverse events experienced by these 2 subjects were considered by the investigator to be unrelated to treatment. No deaths or other serious adverse events occurred during the study. No hematology, chemistry, urinalysis, vital sign, physical examination finding, or change in ECG result was considered clinically meaningful or was reported as an adverse event.
CONCLUSIONS: • For both pioglitazone and metformin, the 90% CIs of the LS mean ratios (test/reference) for AUC(0-tlqc), AUC(0-inf), and Cmax were within the 80% to 125% range required to establish bioequivalency between the fixed-dose combination tablet (1 AD-4833XT tablet) and the individual commercial tablets (1 pioglitazone 15 mg tablet and 1 metformin XT 1000 mg tablet). • Both treatments appeared to be safe and well tolerated as administered in this study.
Date of Report: 21 September 2005

2) Bioequivalence study

Title of Study: An Open-Label, Randomized, 2-Period Crossover Study to Determine the Bioequivalence of 30 mg Pioglitazone and 1000 mg Metformin HCl Extended Release (XT) When Administered as a Fixed-Dose Combination Product or Concomitantly as Commercial Tablets	
Name of Sponsor: Takeda Global Research & Development Center, Inc.	
Name of Finished Product: AD-4833XT (pioglitazone hydrochloride/metformin hydrochloride XT fixed-dose combination product)	
Investigator: (b) (4)	**Study Center:** (b) (4)
Publications Based on the Study: None	
Study Period: 29 April 2005 to 13 May 2005	**Phase of Development:** Phase 1
OBJECTIVES **Primary:** The primary objective of this study was to determine the bioequivalence of a single oral dose of AD-4833XT relative to concomitant administration of the commercial pioglitazone and metformin XT tablets. **Secondary:** The secondary objective of this study was to evaluate the safety of AD-4833XT and the concomitant administration of the commercial pioglitazone and metformin XT tablets.	
METHODS This was a phase 1, open-label, randomized, 2-sequence, 2-period crossover, bioequivalence study. Subjects were assigned randomly to 1 of 2 sequences, and received a single oral dose of test treatment (1 AD-4833XT tablet) and a single oral dose of reference treatment (1 pioglitazone 30 mg commercial tablet and 1 metformin XT 1000 mg commercial tablet) in the fed state. A washout interval of 7 days separated the 2 treatments. Blood samples for the measurement of pioglitazone and metformin concentrations in serum were collected at specified times up to 48 hours after each treatment.	

Title of Study:

An Open-Label, Randomized, 2-Period Crossover Study to Determine the Bioequivalence of 30 mg Pioglitazone and 1000 mg Metformin HCl Extended Release (XT) When Administered as a Fixed-Dose Combination Product or Concomitantly as Commercial Tablets

Schematic of the Study Design

Pretreatment (a)			Treatment (a)				Final Visit
Screening	Baseline	Randomization	Period 1		Period 2		
Days -28 to -2	Day(s) -1 and/or 1	Day 1	Day 1	Days 2 to 7	Day 1	Day 2	Day 3
			T (n=32) (b)	Washout	R		
			R (n=32) (b)		T		

T=Test treatment (1 AD-4833XT tablet).
R=Reference treatment (1 pioglitazone 30 mg commercial tablet and 1 metformin XT 1000 mg commercial tablet).
(a) Subjects were admitted to the clinic on Day -1 and Day 7 of Period 1, dosed on Day 1 of each period, and discharged from the clinic on Day 3 of each period. Baseline procedures were performed on Day -1 and/or Day 1 of Period 1.
(b) Planned number of subjects.

Number of Subjects (Planned and Analyzed):

Planned: 64 subjects; 32 subjects per sequence

Analyzed: Pharmacokinetics—58 subjects; Safety—62 subjects.

Diagnosis and Main Criteria for Inclusion:

To qualify for study participation, subjects must have been healthy male subjects or healthy nonpregnant, nonlactating female subjects aged 18 to 55 years, inclusive; been willing to sign the informed consent form; had clinical laboratory results within the reference ranges or that were acceptable to the investigator; weighed at least 110 pounds (50 kg) and had a body mass index ≤30 kg/m^2; and had negative hepatitis panel and human immunodeficiency virus test results at Screening.

Test Product, Dose and Mode of Administration, Lot Number:

Drug	Dose	Form	Route	Lot No.
AD-4833XT	Pioglitazone hydrochloride 30 mg/ metformin hydrochloride XT 1000 mg	Fixed-dose combination tablet	Oral	573R023A

Duration of Treatment:

The duration of the study for a subject who completed both treatments was 11 days.

Reference Therapy, Dose and Mode of Administration, Lot Number:

Drug	Dose	Form	Route	Lot No.
Pioglitazone hydrochloride (ACTOS®)	30 mg	Commercial tablet	Oral	A10330
Metformin hydrochloride XT (FORTAMET™)	1000 mg	Commercial tablet	Oral	575V002A

Title of Study:

An Open-Label, Randomized, 2-Period Crossover Study to Determine the Bioequivalence of 30 mg Pioglitazone and 1000 mg Metformin HCl Extended Release (XT) When Administered as a Fixed-Dose Combination Product or Concomitantly as Commercial Tablets

Criteria for Evaluation:

Pharmacokinetic:

The area under the concentration-time curve from time 0 to time of last quantifiable concentration (AUC[0-tlqc]), area under the concentration-time curve from time 0 to infinity (AUC[0-inf]), maximum observed concentration (Cmax), time at which Cmax occurred (Tmax), terminal-phase elimination rate constant (λz), and terminal elimination half-life (T1/2) were calculated for each subject from serum concentrations of unchanged pioglitazone and metformin for each treatment using a noncompartmental approach. Actual sampling times rather than scheduled sampling times were used in the computations of pharmacokinetic parameters.

Safety:

Safety variables were adverse events, clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings.

Statistical Methods:

Pharmacokinetic Analysis:

Descriptive statistics (ie, number of subjects, mean, SD, coefficient of variation, median, minimum, and maximum) were used to summarize serum concentrations by treatment and scheduled time of sampling for pioglitazone and metformin, and AUC(0-tlqc), AUC(0-inf), Cmax, Tmax, λz, and T1/2 of pioglitazone and metformin for each treatment. The pharmacokinetic parameters were also summarized by 25th and 75th percentile and SE. Geometric means were computed for AUC(0-tlqc), AUC(0-inf), and Cmax only.

An AUC(0-tlqc)/AUC(0-inf) ratio was determined for each subject. If the AUC(0-tlqc) value comprised less than 80% of the AUC(0-inf) value for an individual subject, that subject's AUC(0-inf) was not included in the descriptive statistics or bioequivalence assessment. An r^2 value for λz was also determined for each subject. If the r^2 value for an individual subject was less than 0.80, that subject's AUC(0-inf), λz, and T1/2 values were not included in the descriptive statistics or bioequivalence assessment.

An analysis of variance with fixed effects for sequence, period, treatment, and random effect for subject nested within sequence was performed on λz and the natural logarithms of AUC(0-tlqc), AUC(0-inf), and Cmax of pioglitazone and metformin; the Wilcoxon signed-rank test was performed on Tmax.

The 90% confidence intervals (CIs) for the ratios of the least-squares (LS) mean for the test treatment (1 AD-4833XT tablet) to the LS mean for the reference treatment (1 pioglitazone 30 mg commercial tablet and 1 metformin XT 1000 mg commercial tablet) were provided for the natural logarithms of AUC(0-tlqc), AUC(0-inf), and Cmax. The test treatment was considered bioequivalent to the reference treatment if the 90% CIs for AUC(0-tlqc), AUC(0-inf), and Cmax of pioglitazone and metformin were within the 80% to 125% bioequivalence range.

Safety Analysis:

Safety variables (adverse events, clinical laboratory evaluations, vital sign measurements, 12-lead ECG results, and physical examination findings), and other safety assessments (medical history findings, concurrent medical conditions, medication history, and concomitant medications) were summarized with descriptive statistics, if appropriate. Abnormal laboratory values for hematology and chemistry tests, and urinalyses, were tabulated by individual subject. Vital sign measurements that met the criteria for very low or very high values were also summarized.

Title of Study:

An Open-Label, Randomized, 2-Period Crossover Study to Determine the Bioequivalence of 30 mg Pioglitazone and 1000 mg Metformin HCl Extended Release (XT) When Administered as a Fixed-Dose Combination Product or Concomitantly as Commercial Tablets

SUMMARY OF RESULTS

Subject Disposition:

Sixty-two subjects (mean age of 31.8 years), 36 men and 26 women, were assigned randomly to treatment at 1 site and received at least 1 dose of study drug. Fifty-eight subjects completed the study. Two subjects received the reference treatment (1 pioglitazone 30 mg commercial tablet and 1 metformin XT 1000 mg commercial tablet) in Period 1, and 1 subject received both the test (1 AD-4833XT tablet) and the reference treatments, then voluntarily withdrew consent and discontinued participation in the study. One other subject received the reference treatment in Period 1, but was withdrawn from the study because of a positive urine drug screen.

Pharmacokinetic Results:

The 90% CIs for the ratios of the LS means for AUC(0-tlqc), AUC(0-inf), and Cmax of pioglitazone and metformin were within the 80% to 125% bioequivalence range and met the criteria for bioequivalence. Therefore the test treatment (1 AD-4833XT tablet) was bioequivalent to the reference treatment (1 pioglitazone 30 mg commercial tablet and 1 metformin XT 1000 mg commercial tablet).

Title of Study:

An Open-Label, Randomized, 2-Period Crossover Study to Determine the Bioequivalence of 30 mg Pioglitazone and 1000 mg Metformin HCl Extended Release (XT) When Administered as a Fixed-Dose Combination Product or Concomitantly as Commercial Tablets

Statistical Analysis of Pharmacokinetic Parameters for Pioglitazone and Metformin

Parameter (units) (a)	n	Treatment	LS Mean (b)	LS Mean Ratio of T/R (90% CI) (%)
Pioglitazone				
AUC(0-inf) (ng·hr/mL)	55	T R	7936.372 8929.429	88.88 (84.97, 92.97)
AUC(0-tlqc) (ng·hr/mL)	57	T R	7503.776 8464.867	88.65 (84.72, 92.75)
Cmax (ng/mL)	57	T R	743.67 832.65	89.31 (83.97, 95.00)
Tmax (hr) (c)	57	T R	3.00 3.00	N/A
λz (1/hr) (c)	55	T R	0.12013 0.10808	N/A
Metformin				
AUC(0-inf) (ng·hr/mL)	54	T R	12256.946 12266.902	99.92 (95.18, 104.89)
AUC(0-tlqc) (ng·hr/mL)	58	T R	11933.460 11892.614	100.34 (95.72, 105.19)
Cmax (ng/mL)	58	T R	1284.54 1280.23	100.34 (96.42, 104.42)
Tmax (hr) (d)	58	T R	8.000 7.008	N/A
λz (1/hr) (d)	54	T R	0.07839 0.07827	N/A

T=Test treatment (1 AD-4833XT tablet).
R=Reference treatment (1 pioglitazone 30 mg commercial tablet and 1 metformin XT 1000 mg commercial tablet).
N/A=not applicable.
(a) An analysis of variance with fixed effects for sequence, period, treatment, and random effect for subject nested within sequence was performed on λz and the natural logarithms of AUC(0-tlqc), AUC(0-inf), and Cmax of pioglitazone and metformin; the Wilcoxon signed rank test was performed on Tmax.
(b) Median values are presented for Tmax.
(c) Tmax: P=0.115, λz: P=0.006.
(d) Tmax: P=0.137, λz: P=0.980.

Title of Study:

An Open-Label, Randomized, 2-Period Crossover Study to Determine the Bioequivalence of 30 mg Pioglitazone and 1000 mg Metformin HCl Extended Release (XT) When Administered as a Fixed-Dose Combination Product or Concomitantly as Commercial Tablets

Safety Results:

Fourteen of 59 subjects (23.7%) experienced 1 or more adverse events following administration of the test treatment (1 AD-4833XT tablet), and 20 subjects of 62 (32.3%) experienced 1 or more adverse events following administration of the reference treatment (1 pioglitazone 30 mg commercial tablet and 1 metformin XT 1000 mg commercial tablet).

Eleven of 59 subjects (18.6%) experienced treatment-emergent adverse events following administration of the test treatment (1 AD-4833XT tablet) that were considered by the investigator to be possibly related to study drug; these were abdominal distension, abdominal pain upper, abdominal pain lower, constipation, flatulence, loose stools, nausea, vomiting, chills, feeling hot, heart rate increased, decreased appetite, dizziness, headache, and tremor.

Fourteen of 62 subjects (22.6%) experienced treatment-emergent adverse events following administration of the reference treatment (1 pioglitazone 30 mg commercial tablet and 1 metformin XT 1000 mg commercial tablet) that were considered by the investigator to be possibly related to study drug; these were abdominal pain upper, abdominal pain lower, constipation, dyspepsia, loose stools, nausea, back pain, dizziness, and headache.

The majority of subjects experienced adverse events that were considered by the investigator to be possibly related to treatment, and all adverse events were considered mild in severity. No deaths, other serious adverse events, or discontinuations due to adverse events occurred during the study.

No hematology, serum chemistry, urinalysis, physical examination, or ECG result was considered clinically meaningful or was reported as an adverse event. Increased heart rate (mild) was reported as an adverse event for Subjects 010 and 026.

CONCLUSIONS

- For both pioglitazone and metformin, the 90% CIs of the LS mean ratios (test/reference) for AUC(0-tlqc), AUC(0-inf), and Cmax were within the 80% to 125% range required to establish bioequivalency between the fixed-dose combination tablet (1 AD-4833XT tablet) and the individual commercial tablets (1 pioglitazone 30 mg tablet and 1 metformin XT 1000 mg tablet).
- The test treatment (1 AD-4833XT tablet) and the reference treatment (1 pioglitazone 30 mg commercial tablet and 1 metformin XT 1000 mg commercial tablet) appeared to be safe and well tolerated as administered in this study.

Date of Report:

28 September 2005

3) Food Effect study

2.0 SYNOPSIS

Title of Study: An Open-Label, Randomized, Crossover Study to Determine the Effect of Food on the Pharmacokinetics of 30 mg Pioglitazone and 1000 mg Extended-Release (XT) Metformin HCl When Administered as a Fixed-Dose Combination Product	
Name of Sponsor: Takeda Global Research & Development Center, Inc.	
Name of Finished Product: AD-4833XT (pioglitazone hydrochloride 30 mg/metformin hydrochloride XT 1000 mg fixed-dose combination product)	
Investigator: (b) (4)	**Study Center:** (b) (4)
Publication Based on the Study: None	
Study Period: 4 May 2005 to 13 May 2005	**Phase of Development:** Phase 1
OBJECTIVES **Primary:** The primary objective of this study was to evaluate the effect of food on the absorption of pioglitazone and metformin from the AD-4833XT fixed-dose combination product relative to administration in a fasted state. **Secondary:** The secondary objective of this study was to evaluate the safety of AD-4833XT.	
METHODS This was a single-center, open-label, randomized, 2-period crossover study. Subjects were assigned randomly to 1 of 2 sequences (12 subjects per sequence), and received a single oral dose of AD-4833XT in the fasted state (reference treatment) and a single oral dose of AD-4833XT after a high-calorie, high-fat meal (test treatment). A washout interval of 7 days separated the 2 treatments. Blood samples for the measurement of pioglitazone and metformin concentrations in serum were collected at specified times up to 48 hours after each treatment.	

Title of Study:

An Open-Label, Randomized, Crossover Study to Determine the Effect of Food on the Pharmacokinetics of 30 mg Pioglitazone and 1000 mg Extended-Release (XT) Metformin HCl When Administered as a Fixed-Dose Combination Product

Schematic of the Study Design

Pretreatment		Treatment				Final Visit
Screening	Baseline/Randomization	Period 1 (a)		Period 2 (a)		
Days -28 to -2	Day -1	Day 1	Days 2 - 7	Day 1	Day 2	Day 3
		R n=12	Washout	T		
		T n=12		R		

T=Test treatment (AD-4833XT in fed state).
R=Reference treatment (AD-4833XT in fasted state).
(a) Subjects were admitted to the clinic on Day -1, and were dosed on Day 1 of each Period. Subjects were discharged from the clinic on Day 3 of each Period.

Number of Subjects (Planned and Analyzed):

Planned: 24 subjects; 12 subjects per sequence.

Analyzed: Pharmacokinetics—24 subjects; Safety—24 subjects.

Diagnosis and Main Criteria for Inclusion:

To qualify for study participation, subjects must have been healthy male subjects or healthy nonpregnant, nonlactating female subjects aged 18 to 55 years, inclusive; been willing to sign the informed consent form; had clinical laboratory results within the reference ranges or that were acceptable to the investigator; weighed at least 110 pounds (50 kg) and had a body mass index less than or equal to 30 kg/m^2; and had negative hepatitis panel and human immunodeficiency virus test results at Screening.

Test Product, Dose and Mode of Administration, Lot Number:

Drug	Dose	Form	Route	Lot Number
AD-4833XT (in fed state)	Pioglitazone hydrochloride 30 mg/ metformin hydrochloride XT 1000 mg	Fixed-dose combination tablet	Oral	573R023B

Duration of Treatment:

The duration of the study for a subject who completed both treatments was 10 days, excluding Baseline Day -1.

Reference Therapy, Dose and Mode of Administration, Lot Number:

Drug	Dose	Form	Route	Lot Number
AD-4833XT (in fasted state)	Pioglitazone hydrochloride 30 mg/ metformin hydrochloride XT 1000 mg	Fixed-dose combination tablet	Oral	573R023B

Title of Study:

An Open-Label, Randomized, Crossover Study to Determine the Effect of Food on the Pharmacokinetics of 30 mg Pioglitazone and 1000 mg Extended-Release (XT) Metformin HCl When Administered as a Fixed-Dose Combination Product

Criteria for Evaluation:

Pharmacokinetic:

The area under the concentration-time curve from time 0 to time of last quantifiable concentration (AUC[0-tlqc]), area under the concentration-time curve from time 0 to infinity (AUC[0-inf]), maximum observed concentration (Cmax), time at which Cmax occurred (Tmax), terminal phase elimination rate constant (λz), and terminal elimination half-life (T1/2) were calculated for each subject from serum concentrations of unchanged pioglitazone and metformin for each treatment using a noncompartmental approach. Actual sampling times rather than scheduled sampling times were used in the computations of pharmacokinetic parameters.

Safety:

Safety variables were adverse events, clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings.

Statistical Methods:

Pharmacokinetic Analysis:

Descriptive statistics (eg, number of subjects, mean, SD, coefficient of variation, 25th percentile, median, 75th percentile, minimum, and maximum) were used to summarize AUC(0-tlqc), AUC(0-inf), Cmax, Tmax, λz, and T1/2 of pioglitazone and metformin for each treatment.

The AUC(0-tlqc)/AUC(0-inf) ratios were determined for each subject. If the AUC(0-tlqc) value comprised less than 80% of the AUC(0-inf) value for an individual subject, that subject's AUC(0-inf) value was not included in the descriptive statistics or food effect analysis. The r^2 value was also calculated for each subject; if the r^2 value was less than 0.80, that subject's λz, T1/2 and AUC(0-inf) values were not included in the descriptive statistics or food effect analysis. Geometric means were computed for AUC(0-tlqc), AUC(0-inf), and Cmax.

Statistical analyses were performed on Tmax, λz, and the natural logarithms of AUC(0-tlqc), AUC(0-inf), and Cmax of pioglitazone and metformin. The analysis of variance model included fixed effects for sequence, period, and treatment, and a random effect for subject nested within sequence. The Wilcoxon signed rank test was performed on Tmax.

To assess the effect of food, the 90% confidence intervals (CIs) for the test/reference (AD-4833XT in fed state/AD-4833XT in fasted state) least squares (LS) mean ratio were provided for natural logarithms of Cmax, AUC(0-inf), and AUC(0-tlqc). The 90% CIs were obtained by using the antilog of the 90% CI for the difference between the LS means on the natural logarithmic scale. If the 90% CIs for Cmax, AUC(0-tlqc), and AUC(0-inf) for pioglitazone and metformin were within the 80% to 125% range, no food effect could be claimed.

Safety Analysis:

Safety variables (adverse events, clinical laboratory evaluations, vital sign measurements, 12-lead ECG results, and physical examination findings), and other safety assessments (medical history findings, concurrent medical conditions, medication history, and concomitant medications) were summarized with descriptive statistics, if appropriate. Abnormal laboratory values for hematology and chemistry tests, and urinalyses, were tabulated by individual subject. Vital sign measurements that met the criteria for very low or very high values were also summarized.

Title of Study:

An Open-Label, Randomized, Crossover Study to Determine the Effect of Food on the Pharmacokinetics of 30 mg Pioglitazone and 1000 mg Extended-Release (XT) Metformin HCl When Administered as a Fixed-Dose Combination Product

SUMMARY OF RESULTS

Subject Disposition, Age, and Sex:

Twenty-four subjects (mean age of 34.0 years), 10 men and 14 women, were assigned randomly to treatment, 12 to each treatment sequence, at a single study site. All 24 subjects completed the study.

Pharmacokinetic Results:

For pioglitazone, the 90% CIs of the fed/fasted LS mean ratios for AUC(0-tlqc) and AUC(0-inf) were within the 80% to 125% range, indicating that total exposure of pioglitazone was not altered when AD-4833XT was administered with food. A decrease of approximately 18% in Cmax was observed after administration of AD-4833XT with food (based on fed/fasted LS mean ratios); the lower limit of the 90% CI for the fed/fasted LS mean ratio for Cmax was below the 80% to 125% range.

There was a statistically significant ($P<0.001$) increase in the median Tmax for pioglitazone of approximately 3 hours when AD-4833XT was administered with food.

For metformin, increases of approximately 85%, 100%, and 98% in AUC(0-inf), AUC(0-tlqc), and Cmax, respectively, were observed when AD-4833XT was administered with food (based on fed/fasted LS mean ratios). The 90% CIs for these ratios were all above the 80% to 125% range, indicating that peak and total exposure of metformin increased when AD-4833XT was administered with food.

There was a statistically significant ($P<0.001$) increase in the median Tmax for metformin of approximately 2 hours when AD-4833XT was administered with food.

Title of Study:

An Open-Label, Randomized, Crossover Study to Determine the Effect of Food on the Pharmacokinetics of 30 mg Pioglitazone and 1000 mg Extended-Release (XT) Metformin HCl When Administered as a Fixed-Dose Combination Product

Statistical Analysis of Pharmacokinetic Parameters for Pioglitazone and Metformin

Parameter (units) (a)	n	Treatment	LS Mean (b)	LS Mean Ratio of T/R (90% CI) (%)
Pioglitazone				
AUC(0-inf) (ng·hr/mL)	24	T R	9452.170 9902.787	95.45 (82.74, 110.11)
AUC(0-tlqc) (ng·hr/mL)	24	T R	8695.991 9261.217	93.90 (80.24, 109.87)
Cmax (ng/mL)	24	T R	880.54 1078.95	81.61 (70.63, 94.30)
Tmax (hr) (c)	24	T R	4.000 1.008	N/A
λz (1/hr) (c)	24	T R	0.11365 0.11287	N/A
Metformin				
AUC(0-inf) (ng·hr/mL)	21	T R	9776.216 5293.188	184.69 (155.23, 219.75)
AUC(0-tlqc) (ng·hr/mL)	24	T R	9832.542 4903.882	200.51 (170.01, 236.47)
Cmax (ng/mL)	24	T R	1117.94 565.13	197.82 (160.30, 244.12)
Tmax (hr) (d)	24	T R	6.000 4.008	N/A
λz (1/hr) (d)	22	T R	0.13513 0.09899	N/A

T=Test treatment (1 AD-4833XT tablet in fed state).
R=Reference treatment (1 AD-4833XT tablet in fasted state).
N/A=not applicable.
(a) An analysis of variance with fixed effects for sequence, period, treatment, and random effect for subject nested within sequence was performed on λz and the natural logarithms of AUC(0-tlqc), AUC(0-inf), and Cmax of pioglitazone and metformin; the Wilcoxon signed rank test was performed on Tmax.
(b) Median values are presented for Tmax.
(c) P-values for treatment effect were <0.001 for Tmax and 0.887 for λz.
(d) P-values for treatment effect were <0.001 for Tmax and 0.019 for λz.

Title of Study:

An Open-Label, Randomized, Crossover Study to Determine the Effect of Food on the Pharmacokinetics of 30 mg Pioglitazone and 1000 mg Extended-Release (XT) Metformin HCl When Administered as a Fixed-Dose Combination Product

Safety Results:

Adverse events were reported for 8 of 24 (33.3%) subjects after administration of the test treatment (1 AD-4833XT tablet in fed state) and for 8 of 24 (33.3%) subjects after administration of the reference treatment (1 AD-4833XT tablet in fasted state).

Of the subjects who experienced adverse events, the majority experienced events that were considered by the investigator to be possibly related to treatment and events that were in the gastrointestinal disorders or nervous system disorders system organ class. The only adverse events reported by more than 1 subject were loose stools (2 subjects), stomach discomfort (2 subjects), fatigue (2 subjects), and dizziness (3 subjects). The events of loose stools and stomach discomfort were considered by the investigator to be possibly related to treatment. The events of fatigue and dizziness were considered either possibly related or unrelated to study drug.

All but 1 adverse event were considered mild in severity, and no adverse events were considered severe. The 1 adverse event reported as moderate, a headache, occurred in Subject 021 approximately 3 hours after receiving the reference treatment (1 AD-4833XT tablet in fasted state) on Day 1 of Period 2. The event resolved within 12 hours without treatment, and was considered by the investigator to be possibly related to treatment.

No deaths, other serious adverse events, or discontinuations due to adverse events occurred during the study.

CONCLUSIONS:

- Relative to dosing in the fasted state, total exposure (AUC[0-inf]) of pioglitazone was not altered when administered with a high-fat meal.
- Relative to dosing in the fasted state, peak exposure (Cmax) of pioglitazone was decreased by approximately 18% when administered with a high-fat meal. This decrease in Cmax was not considered clinically significant.
- Relative to dosing in the fasted state, peak (Cmax) and total (AUC[0-inf]) exposures of metformin were increased by approximately 98% and 85%, respectively, when administered with a high-fat meal. Consistent with the dosing recommendations for metformin extended-release tablets (FORTAMET™), it is recommended that AD-4833XT be taken with an evening meal.
- AD-4833XT appeared to be safe and well tolerated as administered in this study.

Date of Report:

10 October 2005

C OCP Filing Memo

5.1.1 Office of Clinical Pharmacology and Biopharmaceutics

6 *New Drug Application Filing and Review Form*

6.1.1.1.1 General Information About the Submission

	Information		Information
NDA Number	**22-024**	**Brand Name**	**Actoplusmet ™ XR**
OCP Division	**2**	**Generic Name**	**Pioglitazone/metformin extended release**
Medical Division	**DMEP**	**Drug Class**	**Thiazolidinedione/Biguanide**
OCPB Reviewer	**Jayabharathi Vaidyanathan, Ph.D.**	**Indication(s)**	**Type 2 diabetes**
OCPB Team Leader	**Hae-Young Ahn, Ph.D.**	**Dosage Form**	**15 mg/ 1000mg; 30 mg/ 1000 mg tablets**
		Dosing Regimen	**QD**
Date of Submission	**3/31/06**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**12/3/06**	**Sponsor**	**Takeda**
PDUFA Due Date	**2/3/07**	**Priority Classification**	**Standard**
6.1.1.2 Division Due Date	**1/3/07**		

6.1.1.2.1.1.1.1 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
6.2 Healthy Volunteers-				
single dose:				
multiple dose:				
6.2.1 Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	2	2	Actoplusmet XR vs. individual components
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	1	**1**	
Dissolution:	**X**			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**	**3**	
6.2.1.1.1.1				

6.2.1.1.1.2 Filability and QBR comments		
6.2.1.2	**"X" if yes**	6.2.1.2.1.1.1.1 Comments
6.2.1.3 Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable)
6.2.1.4 Comments sent to firm ?		
6.2.1.5		
QBR questions (key issues to be considered)	1) Does food alter the bioavailability of actoplusmetXR? 2) Is the combination formulation of pioglitazone and metformin XR (15 mg/1000 mg and 30 mg/1000 mg) bioequivalent to individual commercially available tablets? 3) Have the analytical methods been sufficiently validated?	

Other comments or information not included above	**Since no clinical trial was conducted with the combination tablet strength proposed in this NDA submission, it is desirable to conduct DSI inspection on the pivotal BE studies.** Study OPIXT-002 Title of study: An open-label, randomized, 3-period crossover study to determine the bioequivalency of pioglitazone 15 mg and metformin XR 1000 mg when administered as commercial tablets and as a combination product **Clinical site:** (b) (4) **Analytical site**: (b) (4) Study OPIXT-003 Title of study: An open-label, randomized, 3-period crossover study to determine the bioequivalency of pioglitazone 30 mg and metformin XR 1000 mg when administered as commercial tablets and as a combination product **Clinical site:** (b) (4) **Analytical site**: (b) (4)
Primary reviewer Signature and Date	**Jaya bharathi Vaidyanathan, Ph.D.**
Secondary reviewer Signature and Date	**Hae-Young Ahn, Ph.D.**

Background:

On March 31, 2006, Takeda submitted NDA 22-024 for pioglitazone/metformin extended release tablets mg for the treatment of type 2 diabetes. Two doses of the pioglitazone/metformin fixed-dose tablet (15 mg/1000 mg and 30 mg/1000 mg) are proposed. Tablets used in pivotal bioequivalence studies were identical in composition to those intended for commercial use. Three studies have been submitted under the clinical pharmacology section as follows.

- An open-label, randomized, crossover, food-effect study was conducted to determine the effect of food on the exposure to pioglitazone and metformin after administration of the pioglitazone 15 mg/metformin extended release 1000 mg fixed-dose combination tablet.
- Open-label, randomized, crossover, bioequivalence study to assess the bioequivalence of the pioglitazone 15 mg/metformin extended release 1000 mg fixed-dose combination tablets to that of separate pioglitazone 15 mg and metformin XR 1000 mg tablets.
- Open-label, randomized, crossover, bioequivalence study to assess the bioequivalence of the pioglitazone 30 mg/metformin extended release 1000 mg fixed-dose combination tablets to that of separate pioglitazone 15 mg and metformin XR 1000 mg tablets.
-

Conclusions: The Clinical Pharmacology section of this application is filable.

D DSI Audit Report

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 27, 2006

TO: David Orloff, M.D.
Director
Division of Metabolism and Endocrine Drug Products

FROM: Jagan Mohan R. Parepally, Ph.D.
Staff Fellow
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. _____
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 22-024, Actoplus Met XR (Pioglitazone HCl and Metformin HCl extended release) Tablets, Sponsored by Takeda Global Research & Development Center, Inc.

At the request of the Division of Metabolism and Endocrine Drug Products (DMEDP), the Division of Scientific Investigations (DSI) conducted an audit of the clinical and analytical portions of following bioequivalence studies:

Study 01-04-TL-OPIXT-002: An Open-Label, Randomized, 2-Period Crossover Study to Determine the Bioequivalence of 15 mg Pioglitazone and 1000 mg Metformin HCl Extended Release(XT) When Administered as a Fixed-Dose Combination Product or Concomitantly as Commercial Tablets.

Study 01-04-TL-OPIXT-003: An Open-Label, Randomized, 2-Period Crossover Study to Determine the Bioequivalence of 30 mg Pioglitazone and 1000 mg Metformin HCl Extended Release(XT) When Administered as a Fixed-Dose Combination Product or Concomitantly as Commercial Tablets.

The clinical portion of studies 01-04-TL-OPIXT-002 and 01-04-TL-OPIXT-003 were conducted at (b) (4) and (b) (4). Analytical portions of both studies were conducted at (b) (4) (b) (4) Following the inspection of (b) (4)

(December 6-13, 2006) and (b) (4). (December 11-15, 2006), Form FDA-483 was issued (Attachment 1). No objectionable findings were noted and Form FDA-483 was not issued at (b) (4) (b) (4) The objectionable items and our evaluation are provided below:

(b) (4)

1. **An investigation was not conducted in accordance with the investigational plan.**
2. **Failure to prepare or maintain accurate case histories with respect to observations and pertinent to the investigation and informed consent.**

Contrary to the protocol, informed consent and clinical laboratory tests were not obtained at screening for Subject# 1001. Instead, consent and clinical laboratory tests were obtained prior to dosing of the subject. The clinical laboratory results were normal and there were no adverse events reported for the subject during the study. The above protocol deviation does not compromise the safety of the subject. The firm should assure that they follow the protocol in future studies.

Although, informed consent and laboratory tests were not obtained at screening, the case report form (CRF) erroneously states the consent and laboratory tests were done at screening for subject 1001. The firm should assure that CRFs accurately reflect source data for future studies.

(b) (4)

1. **Approximately 90 study samples were re-assayed for Pioglitazone or Metformin due to pharmacokinetic reasons. No objective criteria were established a priori to justify selection of these study samples.**

The finding is unlikely to affect study outcome as less than 1% of the study samples were re-assayed for pharmacokinetic reasons and approximately 88% of the re-assayed samples were within 10% of the original concentrations. Nonetheless, the firm should have

established procedure for selecting pharmacokinetic repeats in future studies.

Conclusion:

DSI recommends that the data obtained from the studies 01-04-TL-OPIXT-002 and 01-04-TL-OPIXT-003 be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Jagan Mohan R. Parepally, Ph.D.

Final Classifications:

(b) (4) **- VAI**
(b) (4) **- NAI**
(b) (4) **- VAI**

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/s/

Jagan Parepally
12/27/2006 02:36:38 PM
PHARMACOLOGIST
Dr. Viswanathan signed the paper copy on 12/27/2006

C.T. Viswanathan
12/27/2006 02:48:15 PM
BIOPHARMACEUTICS

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/s/

Jayabharathi Vaidyanathan
1/3/2007 07:52:42 AM
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Xiao-xiong Wei
1/4/2007 09:16:05 AM
BIOPHARMACEUTICS