Appendix 1

A study to determine the effects of multiple-dose cilostazol tablets on single dose lovastatin pharmacokinetics in healthy subjects

Study 21-98-208-01

Report issued: August 31, 1998

Study initiated: August 6th, 1998
Study terminated: August 16th, 1998

Investigator: James Kisicki, M.D.

Study objective:

To determine the effects of cilostazol on the pharmacokinetics of lovastatin.

Study medication:

100 mg cilostazol tablets (lot # 6C73PA1)
50 mg cilostazol tablets (lot # 7K89PB1)
40 mg lovastatin tablets (lot # E1335)

Study population:

Fifteen subjects were enrolled in the study but 13 subjects completed the study.

Study design:

This was an open-label, multiple dose, sequential treatment study, to determine the effect of coadministration of cilostazol on lovastatin pharmacokinetics.

Study procedures:

On day 1 a single oral dose of lovastatin 80 mg was administered. On days 2-8, each subject received an oral dose of 100 mg cilostazol-bid. On day 7 (while cilostazol was at steady state), a single oral dose of

lovastatin 80 mg was coadministered with the 100 mg dose of cilostazol. On day 9 of the study, a single oral dose of cilostazol 150 mg was administered concomitantly with an 80 mg dose of lovastatin.

Subjects were fasted 10 hours prior to each morning dose. The drugs were taken with 240 ml tepid water.

Blood samples were collected for the determination of cilostazol and metabolites at the following time points:

Day 1: predose
Day 2: predose
Day 5: predose
Day 6: predose, 2, 3, 4 and 12 hours after dosing
Day 7: predose, 2, 3, 4 and 12 hours after dosing
Day 8: predose
Day 9: predose, 2, 3, 4, 12 and 24 hours (day 10) after dosing

Blood samples were collected for the determination of lovastatin and metabolite at the following time points:

Day 1: predose, 1, 2, 3, 4, 6, 8, 12 and 24 hours (day 2) after dosing
Day 7: predose, 1, 2, 3, 4, 6, 8, 12 and 24 hours (day 8) after dosing
Day 9: predose, 1, 2, 3, 4, 6, 8, 12and 24 hours (day 10) after dosing

Concentration-time data were analyzed using model-independent methods. Pharmacokinetic calculations were performed with WinNonlin Pro software.

Reviewer's comments:

The sampling times are totally inadequate. Cilostazol half-life is reported to be 11 hours and it appears that most of the PK sampling is carried out until 12 hours after dosing, except for the last dose which is carried out until 24 hours post-dose. Additionally, lovastatin half-life is reported in the present study to be range This would have been very difficult to predict accurately, under the present sampling conditions, since determination of the terminal phase rate constant could not be accurately made.

Methods of analysis:

Plasma samples were analyzed for OPC-13013 and its metabolites OPC-13015 and OPC-13213, using a validated method. The samples were analyzed at The assay was linear for cilostazol and its metabolites in the range of in plasma with the LOQ being 20 ng/ml.

Plasma samples were analyzed for lovastatin and its ß-hydroxy-acid metabolite using a validated method. The samples were analyzed at The assay was linear for lovastatin and its ß-hydroxy acid metabolite in the range of ng/ml in plasma with the LOQ being 0.10 ng/ml.

Steady-state pharmacokinetic parameters of cilostazol following 100 mg cilostazol bid were compared on day 6 (cilostazol alone) with day 7 (cilostazol with lovastatin) using a two-tailed paired t-test.

The comparisons of interest were the following: lovastatin plus 100 mg cilostazol versus lovastatin alone; lovastatin plus 150 mg cilostazol versus lovastatin alone. Potential additional effects of cilostazol on lovastatin were assessed by comparing the 100 mg cilostazol PK profile to the 150 mg cilostazol PK profile.

Results:

Of the fifteen subjects that enrolled, 2 subjects (8 and 9) did not complete the study (they did not receive further lovastatin beyond the first dose).

Summary table of PK parameters of cilostazol and lovastatin:

Compound	Cmax (ng/ml)	Tmax (hours)	AUC last (ng.h/ml)	AUC inf (observed)
OPC-13013 (day 6)	1478.3±421.6	2.7±0.9	10835±3252.1	
OPC-13013 (day 7)	1261.1±305.0	2.5±0.7	8616.0±2993.9	
OPC-13013 (day 9)	1927.9±617.1	2.5±1	13359.0±4819.1	
OPC-13015 (day 6)	439.7±122.4	3.1±0.9	4278.5±1403.1	
OPC-13015 (day 7)	426.7±97.1	3.1±0.8	3777.3±1230.7	
OPC-13015 (day 9)	479.4±122.5	3.2±1.1	4443.9±1351.6	
OPC-13213 (day 6)	155.9±48.4	3.0±0.9	1277.9±350.2	
OPC-13213 (day 7)	148.8±39.8	2.9±0.8	1179.0±392.3	
OPC-13213 (day 9)	177.6±78.6	3.2±1.2	1418.1±532.9	
OPC-13217 (day 6)	34.0±13.8	2.8±0.7	229.7±124.5	
OPC-13217 (day 7)	30.1±12.0	2.8+0.8	185.7±130.4	
OPC-13217 (day 9)	34.2±12.8	3.2±0.9	246.6±118.3	
Lovastatin (day 1)	10.7±4.1	1.5±0.7	55.6±32.4	96.4±72.5
Lovastatin (day 7)	8.6±5.8	1.6±0.5	86.6±49.1	165.7±118.6
Lovastatin (day 9)	13.6±8.5	2.0±1.1	86.0±52.3	151.9±76.4
ß-hydroxy (day 1)	7.4±3.0	3.3±0.6	43.3±18.0	59.4±21.9
ß-hydroxy (day 7)	12.4±9.4	3.5±0.8	73.8±45.5	97.1±63.2
ß-hydroxy (day 9)	16.3±7.9	3.5±0.7	87.0±40.8	101.4±45.6

There was a significant difference in cilostazol Cmax ($p=0.041$) and AUC ($p=0.023$) when cilostazol was co-administered with 80 mg of lovastatin,

based on the comparison of day 7 (100 mg of cilostazol plus 80 mg of lovastatin) results with those of day 6 (100 mg cilostazol alone) (Table ST-16). The AUC and Cmax values of cilostazol were lower when cilostazol was administered with lovaststin (day 7), as compared to when cilostazol was administered alone (day 6). There was no significant change in the cilostazol metabolite PK profile upon coadministration of cilostazol with lovastatin.

Lovastatin and its ß-hydroxy metabolite plasma concentration time profiles are provided in figure 6.5.1. Additionally, the mean PK parameters for lovastatin and its metabolite are provided in the table above as well as in table 6.5.1.

The results show that the PK of lovastatin and that of its active metabolites were significantly different when administered alone compared with when administered with cilostazol. The mean AUC(t) and AUC (inf) of lovastatin increased by 56% and 72%, respectively, when comparing day 7 (cilostazol 100 mg plus lovastatin) to day 1 (lovastatin alone) and the same parameters were increased by 55 and 58% when comparing day 9 (cilostazol 150 mg plus lovastatin) with day 1 (lovastatin alone). Additionally, the Cmax of lovastatin increased by 58% when cilostazol dose was increased from 100 mg to 150 mg. The Cmax, AUC(t) and AUC(inf) values for the ß-hydroxy metabolite of lovastatin increased significantly when cilostazol was co-administered with lovastatin. However, these values did not rise further when the dose of cilostazol was increased to 150 mg. The increases ranged of the values from day 1 (lovastatin alone).

Reviewer's comments:

There are unacceptable differences between AUC(t) and AUC(inf) for lovastatin and its metabolite. The difference ranges from for lovastatin and for its active ß-hydroxy metabolite. These large differences between AUC(t) and AUC(inf) are most likely due to the inadequate PK sampling time points which did not go out far enough until the drug plasma levels had declined by at least 3 half-lives.

Discussion:

The rate and extent of cilostazol absorption decreased by 15 and 20%, respectively, when 100 mg cilostazol was coadministered with 80 mg

lovastatin. No effect was noted on the PK profile of the metabolites of cilostazol, when the drug was coadministered with lovastatin.

Lovastatin is reported to be a weak substrate for CYP3A4 with a Km of 340 μM. Therefore, CYP3A4 inhibitors and substrates may alter the clearance of lovastatin. An increase in the serum concentrations of lovastatin may lead to an increased risk of skeletal muscle toxicity. In fact, it is reported that grapefruit juice and itraconazole can increase serum lovastatin levels by 12-20 fold.

Previous in vitro studies conducted by the sponsor had shown a discrepancy in the inhibition by cilostazol of cDNA-expressed CYP3A4 and microsomal CYP3A4 activity. In the 2 in vitro studies, the Ki values were 6 and 19 μM for the cDNA-expressed CYP3A4 inhibition and 100.6μM for the microsomal CYP3A4 inhibition.

Cilostazol at 100mg bid did not increase the Cmax of lovastatin, however, when the concentration of cilostazol was increased to 150 mg, the Cmax of lovastatin was significantly increased by 58% (as compared to when cilostazol was given at 100 mg). The AUC for lovastatin was increased by up to 70% with the coadministration of cilostazol. The sponsor states that the 1.7 fold increase in the exposure to lovastatin is not likely to clinically relevant. This statement will need to be evaluated by the medical reviewer.

Previous studies by the sponsor (study 21095-204) did not show an interaction between cilostazol taken at 100 mg bid for 7 days with R-warfarin (metabolized 46% by CYP1A2, 20% by CYP3A4 and 34% by other P450s). In another study (21-98-205), 3 μg ^{14}C-erythromycin (CYP3A4 substrate) was given as an IV bolus, and the breath test was performed before and after 100 mg bid cilostazol for 5 days. In that study, the AUC(inf) values for the erythromycin breath test did not show any difference between day 1 and day 5 (before and after cilostazol).

Conclusions:

The sponsor concludes that although cilostazol is a potent inhibitor of CYP3A4, the 1.7-fold increase in the exposure to lovastatin is not likely to result in clinically relevant toxicities. The validity of this statement will not be determined in this review. Therefore, the sponsor concludes that a dose reduction of lovastatin is not recommended unless adverse

events persist. In such an event, the sponsor recommends that the dose of lovastatin be decreased to 50 mg, from 80 mg per day. Similarly, the sponsor does not recommend a dose adjustment of cilostazol, even though the Cmax and AUC values tend to significantly decrease (15% and 20%, respectively) with lovastatin coadministration. The validity of this statement will not be evaluated in this review.

It should be noted that the sponsor's conclusions are based on data, the validity of which are in question. In table 6.5.1, the t ½ of lovastatin is said to range between hours. However, the PK sampling time points only go as far as 24 hours after dosing. This is less than one half-life after dosing, and thus grossly inadequate. Consequently, the accuracy of the half-life determinations is in question, since the terminal phase rate constant could not have been accurately calculated. Since the PK sampling time points that were undertaken in this study were inadequate, they do not allow a precise evaluation of the results. Additionally, the difference between AUC(last) and AUC(inf) as reported in the summary table above, show that the differences between these 2 parameters reaches 91%, whereas it is desirable that this difference not exceed 10 %.

Therefore, although the sponsor draws certain conclusions from this study, since the data are not particularly reliable, all conclusions should be interpreted with a note of caution. The clinical relevance of the finding that cilostazol increases the exposure to lovastatin by 1.7 fold is beyond the scope of this review and will be determined by the medical reviewer. However, it is recommended that an advisory statement regarding the potential drug interaction between cilostazol and lovastatin be added in the package insert.

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Figure 6.5-1. Mean Plasma Lovastatin and β-Hydroxy Lovastatin Acid Metabolite Concentration – Time Profiles Following Administration of 80 mg of Lovastatin Alone (Day 1), or 80 mg of Lovastatin Co-administered with 100 mg (Day 7) and 150 mg (Day 9) of Cilostazol, Preceded by 100 mg Cilostazol q12h for at Least 6 Days.

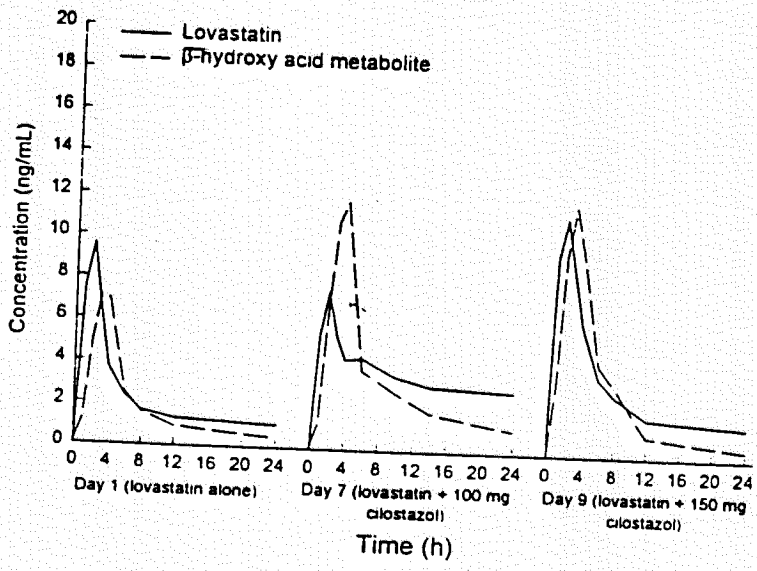

Table 6.5-1. Summary of Mean (CV%) Lovastatin and β-hydroxy Lovastatin Acid Pharmacokinetics for Single Oral 80 mg Lovastatin Doses Either Given Alone (Day 1) or Co-administered with 100 mg (Day 7) or 150 mg (Day 9) of Cilostazol, Preceded by 6 to 8 Days of dosing with 100 mg Cilostazol q12h.

	Lovastatin Alone		Lovastatin + 100 mg Cilostazol		Lovastatin + 150 mg Cilostazol	
	Lovastatin	β-hydroxy acid	Lovastatin	β-hydroxy acid	Lovastatin	β-hydroxy acid
C_{max} (ng/mL)	10.7 (4.1)	7.4 (3.0)	8.6 (5.8)	12.4 (9.4)	13.9 (8.5)	16.3 (7.9)*
t_{max} (h)[1]	1 (1-3)[1]	3 (2-4)	2 (1-2)	4 (2-4)	2 (1-4)	4 (2-4)
$T_{1/2}$ (h)	23.5 (16.1)	15.4 (10.5)	21.7 (8.1)	13.7 (4.7)	31.0 (17.1)	10.8 (4.6)
AUC_T (ng·h/mL)	55.6 (32.4)	43.0 (18.0)	86.6 (49.1)*	73.8 (45.5)*	86.0 (52.3)	87.0 (40.8)*
AUCINF (ng·h/mL)	96.4 (72.5)	59.4 (21.9)	165.7 (118.6)*	97.1 (63.2)	151.9 (76.4)*	101.4 (45.6)*

[1] t_{max} is expressed as median (range)

* Statistically significantly different from lovastatin alone ($p < 0.05$).

ST-14 Statistical Comparison of Lovastatin

Day	Cmax (ng/mL)	Tmax (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
1	10.7 ± 4.1[1]	1 (1-3)[2]	55.6 ± 32.4	96.4 ± 72.5
7	8.6 ± 5.8	2 (1-2)	86.6 ± 49.1	165.7 ± 118.6
9	13.9 ± 8.5	2 (1-4)	86.0 ± 52.3	151.9 ±76.4
p-value contrast	0.083		0.085	0.046
Day 7 vs 1	0.147		0.046	0.049
Day 9 vs 1	0.417		0.067	0.025
Day 9 vs 7	0.029		0.893	0.952

[1] mean ± SD format for Cmax, AUC_t, and AUC excluding Tmax, p-values, and contrasts
[2] median (range) format for Tmax

ST-15 Statistical Comparison of β-hydroxy lovastatin

Day	Cmax (ng/mL)	Tmax (h)	AUC_T (ng·h/mL)	AUC (ng·h/mL)
1	7.4 ± 3.0[1]	3.0 (2-4)[2]	43.0 ± 18.0	59.4 ± 21.9
7	12.4 ± 9.4	4 (2-4)	73.8 ± 45.5	97.1 ± 63.2
9	16.3 ± 7.9	4 (2-4)	87.0 ± 40.8	101.4 ± 45.6
p-value contrast	0.010		0.009	0.068
Day 7 vs 1	0.098		0.028	0.078
Day 9 vs 1	0.003		0.003	0.028
Day 9 vs 7	0.123		0.346	0.625

[1] mean ± SD format for Cmax, AUC_t, and AUC excluding Tmax, p-values, and contrasts
[2] median (range) format for Tmax

AUG 1 1 1999

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20863.
N(PN)051
Cilostazol
Otsuka Pharmaceuticals

Submission Date: June 24, 1998.

Reviewer: Patrick J Marroum.

Type of submission: Response to comments.

BACKGROUND:

Cilostazol (OPC-13013) is a potent inhibitor of platelet aggregation and a peripheral vasodilator. It is being developed for the treatment of intermittent claudication. The original application has been reviewed on June 16, 1998 and a copy of the review was forwarded to the sponsor. Enclosed in this submission in Appendix I are the firm's responses to these comments.

COMMENTS:

1- All the responses to the comments raised in the original review are acceptable.

RECOMMENDATION:

No further action is warranted at this time.

Patrick J Marroum Ph.D. 8/11/1998

RD/FT initialed by Mehul Mehta Ph.D. 8/11/98
cc: NDA, 20863, HFD 110 , HFD 860 (Marroum), CDER document room: Barbara Murphy.

AUG - 5 1998

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20863.
N(PN)048
Cilostazol
Otsuka Pharmaceuticals

Submission Date: June 11, 1998.

Reviewer: Patrick J Marroum.

Type of submission: Amendment to a final report.

BACKGROUND:

Cilostazol (OPC-13013) is a potent inhibitor of platelet aggregation and a peripheral vasodilator. It is being developed for the treatment of intermittent claudication.
As a result from a FDA audit that took place in 4/1998, a form FDA 483 was issued for the following reasons:
-Incorrect reference to Appendix III-7 which does not exists for the following study:" An open label study of the absorption, distribution, metabolism and excretion of cilostazol following oral administration of ^{14}C-Cilostazol in healthy human subjects." The appendix that should be referred to is missing from the original NDA. The final study report has been amended in this submission to add the missing Appendix III-5. In addition the certificate of analysis for the radiolabeled drug product which was inadvertently omitted from the original report is added in Appendix II-5 of the report.

COMMENTS:

1-The study that is amended is a mass balance study that was reviewed in the original NDA review dated June 16, 1998. The amendments included in this submission have been reviewed and do not have any impact on the acceptability of the study.

RECOMMENDATION:

No further action is warranted at this time.

8/5/1998.

Patrick J Marroum Ph.D.

RD/FT initialed by Mehul Mehta Ph.D. MMM 8/5/98
cc: NDA, 20863, HFD 110 , HFD 860 (Marroum), CDER document room: Barbara Murphy.

AUG - 4 1998 G. Buehler

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20863. Submission Date: July 24,1998.
N(PN)061
Cilostazol
Otsuka Pharmaceuticals

Reviewer: Patrick J Marroum.

Type of submission: Protocol for a drug-drug interaction study.

BACKGROUND:

Cilostazol (OPC-13013) is a potent inhibitor of platelet aggregation and a peripheral vasodilator. It is being developed for the treatment of intermittent claudication. Since both cilostazol and clopidogrel act to inhibit platelet aggregation it is necessary to determine whether there is a clinically significant enhancement of bleeding or bleeding complications when both drugs are administered concomitantly. In vitro results have shown conflicting results on whether cilostazol and its metabolites are potent inhibitors of CYP3A4. As a second issue lovastatin is primarily metabolized by CYP3A4. Increased risk of skeletal muscle toxicity of lovastatin is observed with CYP3A4 inhibitors such as ketoconazole and grapefruit juice due to increased plasma concentrations.

Enclosed in this submission are two drug interactions study protocols one with lovastatin the other with clopidogrel. The interaction with lovastatin protocol was reviewed on July 27 1998 and will not be included as part of this review. Appendix I is a summary of the protocol entitled: " A randomized, double blind, parallel group, placebo controlled study of the effects of orally administered clopidogrel and cilostazol in healthy subjects".

COMMENTS:

1-The sponsor should include in the study report a complete description of the assay methodology used to quantitate cilostazol and clopidogrel in plasma. Assay validation data on the within and between day accuracy and precision, specificity and sensitivity as well as linearity should be also included in the study report.

RECOMMENDATION:

The Division of Pharmaceutical Evaluation I finds the above protocol acceptable.

Patrick J Marroum Ph.D. 8/4/1998

RD/FT initialed by Mehul Mehta Ph.D. MMM 8/4/98
cc: NDA, 20863, HFD 110 , HFD 860 (Marroum), CDER document room: Barbara Murphy

JUL 27 1998

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20863.
N(PN)061
Cilostazol
Otsuka Pharmaceuticals

Submission Date: July 23 1998.

Reviewer: Patrick J Marroum.

Type of submission: Protocol for a drug-drug interaction study.

BACKGROUND:

Cilostazol (OPC-13013) is a potent inhibitor of platelet aggregation inhibitor and a peripheral vasodilator. It is being developed for the treatment of intermittent claudication. In vitro studies have shown conflicting results on whether cilostazol and its metabolites are potent inhibitors of CYP3A4. Lovastatin is primarily metabolized by CYP3A4. Increased risk of skeletal muscle toxicity of lovastatin is observed with CYP3A4 inhibitors such as ketoconazole and grapefruit juice due to increased plasma concentrations. Therefore this study is to investigate the potential inhibition of lovastatin metabolism by cilostazol and its metabolites. Enclosed in Appendix I is a summary of the protocol entitled: " A study to determine the effects of multiple dose cilostazol tablets on single dose lovastatin pharmacokinetics in healthy subjects".

COMMENTS:

1-The sponsor should include in the study report a complete description of the assay methodology used to measure cilostazol and lovastatin in plasma. Assay validation data on the within and between accuracy and precision, specificity and sensitivity as well as linearity should be also included in the study report.

RECOMMENDATION:

The Division of Pharmaceutical Evaluation I finds the above protocol acceptable.

Patrick J Marroum Ph.D.

7/27/1998

RD/FT initialed by Mehul Mehta Ph.D. MuM 7/27/98

cc: NDA, 20863, HFD 110 , HFD 860 (Marroum), CDER document room: Barbara Murphy