CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-961

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	21-961
Submission Date(s):	July 28, 2005; March 14, 2006
Brand Name:	TBD
Generic Name:	Simvastatin orally disintegrating tablets
Reviewer:	Sang M. Chung, Ph.D.
Team Leader:	Hae-Young Ahn, Ph.D.
OCP Division:	DCP 2
ORM division:	DMEP
Sponsor:	Synthon Pharmaceuticals, Inc.
Submission Type:	Original NDA, 505(b)(2)
Formulation:	Tablets; 10mg, 20mg, 40mg, and 80mg
Indication:	Treatment of hypercholesterolemia, dyslipidemia, hyperlipidemia, hypertriglyeridemia, dysbetalipoproteinemia

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2 Executive Summary

2.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 21-961 and finds it inconclusive because the study was not acceptable to DSI with numerous compliance issues. In addition, the sponsor is recommended developing a dissolution method and specification to assure characteristics of Simvastatin Orally Disintegrating Tablets. The Recommendation should be sent to the sponsor as appropriate.

2.2 Phase IV Commitments

N/A

2.3 Summary of Clinical Pharmacology Findings

Bioequivalence (BE) of Simvastatin Orally Disintegrating Tablets (ODT) to Zocor was evaluated in a two-way crossover study. The pharmacokinetics of simvastatin and simvastatin acid following ODT were comparable to those following Zocor. However, there were numerous unacceptable compliance issues from the study sites according to DSI inspection. It indicated that the BE of the test product could not be evaluated using the study results. In addition, the dissolution method in the original application was not discriminative enough to characterize ODT formulation. Therefore, it is recommended developing new dissolution method and specification.

3 Question-Based Review (QBR)

3.1 General Clinical Pharmacology

3.1.1 What are the PK characteristics of the drug and the results of BE study?

Orally disintegrating tablet (ODT) is defined "as a solid dosage from containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue" according to the Orange Book. The formulation does not require water to aid swallowing in general. According to the sponsor, the ODT for simvastatin was developed as an easier dosage form for patients who have had difficulties in swallowing conventional dosage forms.

The sponsor submitted this 505(b)(2) to support the new dosage form referencing Zocor®. Bioequivalence (BE) of the simvastatin 80mg ODT to the reference product (Zocor® 80mg tablet) was assessed in a randomized, single dose, two-period study (CSP.US01.SVT.ODT80.001).

Tablets were administered under at least 10 hours fasting condition in healthy subjects. The ODT was administered without the aid of water, and 240 ml of water was administered at 1 minute post-dosing. The reference product was taken with 240 ml of water. Blood samples were obtained until 24 hour post-dose (i.e., predose, at 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 4, 5, 6, 8, 12, 16, and 24 hour) for simvastatin (SVT) and simvastatin acid (SVTA) assay in plasma. Levels of SVT and SVTA in plasma were determined using a HPLC/MS/MS method.

A total of 72 subjects (female=38, male=34) were enrolled for the study and 6 subjects did not complete all the treatments due to common colds, tonsillitis, or non-compliance.

Plasma concentration-time profiles for SVT and SVTA were shown in Figure 1. BE was assessed based on AUC_{0-t}, AUC_{0-inf}, and C_{max} for SVT and SVTA, respectively. The AUC_{0-inf} was calculated in 63 subjects and 64 subjects for SVT and SVTA, respectively, due to non-physiologic terminal elimination rate constant in a few subjects.

The pharmacokinetic parameters for SVT and SVTA were summarized in Table 1 and results of statistical analysis for the BE assessment were summarized in Table 2.

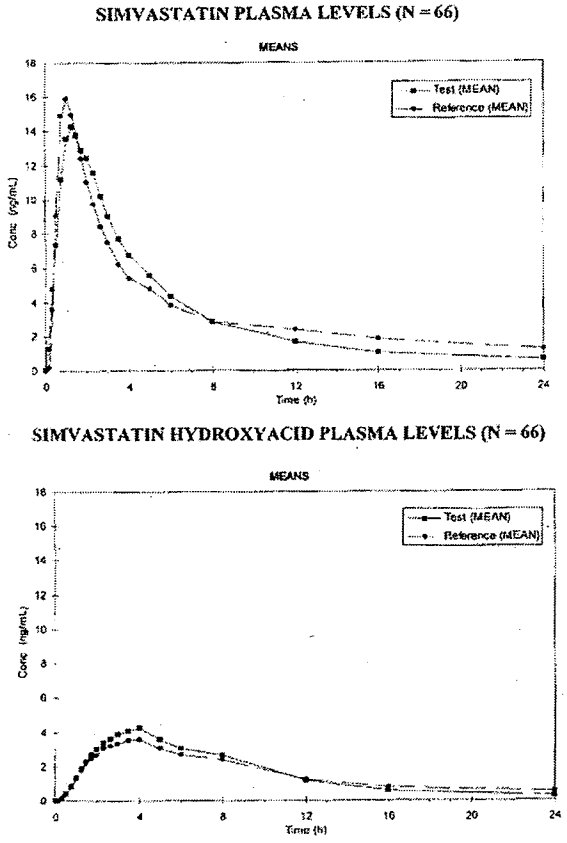

Figure 1 **Plasma concentration-time profiles of Simvastatin (left) and Simvastatin acid (right)**

Table 1 **Summary of pharmacokinetic parameters; Arithmetic mean (%CV)**

Parameter	Test	Reference	T/R (%)
Simvastatin			
AUC $_{0-t}$ (ng h/ml, n=66)	77.61 (48.29)	83.89 (55.86)	92.5
AUC $_{0-\infty}$ (ng h/ml, n=63)	98.50 (105.21)	101.92 (56.57)	96.7
C_{max} (ng/ml, n=66)	18.27 (59.60)	19.44 (78.76)	94.0
t_{max} (hr, n=66)	2.03 (80.27)	1.73 (112.17)	
k_{el} (1/hr, n=63)	0.1496 (67.19)	0.1087 (77.55)	
t_{half} (hr, n=63)	9.39 (180.34)	10.10 (79.30)	
Simvastatin Acid			
AUC $_{0-t}$ (ng h/ml, n=66)	37.67 (57.43)	36.61 (59.30)	103.0
AUC $_{0-\infty}$ (ng h/ml, n=63)	41.54 (56.9)	47.76 (77.03)	87.0
C_{max} (ng/ml, n=66)	4.50 (64.38)	3.88 (59.35)	116.0
t_{max} (hr, n=66)	4.42 (36.22)	4.35 (52.75)	
k_{el} (1/hr, n=63)	0.1554 (45.60)	0.1357 (59.73)	
t_{half} (hr, n=63)	5.95 (79.01)	8.67 (130.29)	

Table 2 **Summary of statistical analysis for the BE assessment: Geometric mean ratios (Test/Reference) and 90% confidence intervals**

Parameter for SVT	Test	Reference	Ratio (%)	90% C.I.
AUC $_{0-t}$ (n=66)	Simvastatin ODT	Zocor®	**95.3**	**88.1 – 103.1**
AUC $_{0-\infty}$ (n=63)	Simvastatin ODT	Zocor®	**90.6**	**81.5 – 100.8**
C_{max} (n=66)	Simvastatin ODT	Zocor®	**104.0**	**92.9 – 116.4**
Parameter for SVTA	**Test**	**Reference**	**Ratio (%)**	**90% C.I.**
AUC $_{0-t}$ (n=66)	Simvastatin ODT	Zocor®	**103.22**	**97.85 – 108.89**
AUC $_{0-\infty}$ (n=64)	Simvastatin ODT	Zocor®	**92.95**	**86.61– 99.77**
C_{max} (n=66)	Simvastatin ODT	Zocor®	**114.45**	**106.38 – 123.13**

The clinical study site and analytical site were as follows, and DSI inspection on the sites was requested:

Clinical study site:

Analytical study site: b(4)

3.2 General Biopharmaceutics

3.2.1 What are the components in the to-be-marketed formulation?

The drug substance was manufactured by [redacted] The information on test and reference formulations was summarized in Table 3. Major components of the test product were proportionally similar across different strengths (Table 4). b(4)

Table 3 Product information

	Test	Reference
Name	Simvastatin 80mg ODT	Zocor® 80mg tablets
Batch number	3118403V3	N5746
Expiry date	May 2005	October 2005
Supplier	Synthon Pharmaceuticals, Ltd, USA	Merck & Co., Inc., USA
Manufacturer	[redacted]	[redacted]
Packaging	[redacted]	[redacted]

b(4)

Table 4 Tablet compositions

Ingredient	Amount (mg)/Tablet				Amount (%) in Tablet			
	10 mg	20 mg	40 mg	80 mg	10 mg	20 mg	40 mg	80 mg
Simvastatin	10.00	20.00	40.00	80.00	14.3	14.3	14.3	14.3
Butylated hydroxyanisole	[redacted]							
Povidone								
Crospovidone								
Weight of								
hydroxypropylcellulose								
Silicified microcrystalline cellulose								
Mint menthol								
Sucralose								
Iron oxide yellow								
Iron oxide red								
Weight of blend								
Glyceryl behenate								
Total mass per tablet								

b(4)

3.2.2 What is the proposed dissolution method?

Dissolution profiles of ODT were characterized using dissolution method for Zocor® with increased paddle speed (75 rpm from 50 rpm) and the study results were summarized in Table 5. It was concluded that the dissolution method of Zocor® was not discriminative enough for ODT.

Table 5 Summary of dissolution studies

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range) 3 min	6 min	10 min	15 min	20 min	30 min	45 min	Study Report Location
[redacted] #2446/04	Simvastatin ODT Lot #3117703V3	10 mg Tablet	Apparatus 2 Rotation: 75 rpm Medium: 0.5% SDS; pH 7.0 Volume: 900 mL Temperature: 37°C	12	85.2 (83.8-89.0)	93.8 (92.6-96.2)	96.8 (95.5-98.5)	98.4 (97.0-101.4)	99.0 (97.6-100.8)	99.3 (97.9-101.2)	99.7 (98.5-101.8)	Module 1, Section 3.9 p. 11
[redacted] #2449/04	Simvastatin ODT Lot #3117903V3	20 mg Tablet		12	84.8 (81.6-87.7)	93.1 (90.0-96.4)	96.3 (93.8-100.0)	98.0 (94.8-101.6)	98.7 (96.0-102.2)	99.2 (96.5-102.7)	99.3 (96.6-102.8)	Module 1, Section 3.9 p. 12
[redacted] #2452/04	Simvastatin ODT Lot #3118203V3	40 mg Tablet		12	86.5 (85.1-89.1)	94.6 (93.1-96.2)	97.4 (96.0-98.7)	98.4 (97.1-99.9)	99.2 (98.0-100.7)	99.3 (97.9-100.8)	99.6 (98.2-100.9)	Module 1, Section 3.9 p. 13
[redacted] #2458/04	Simvastatin ODT Lot #3118403V3	80 mg Tablet		12	85.9 (84.2-87.8)	93.9 (92.2-95.5)	97.0 (94.9-98.8)	98.0 (96.1-99.7)	98.4 (96.5-100.1)	98.6 (96.7-100.3)	98.9 (97.3-100.7)	Module 1, Section 3.9 p. 14

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Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range) 10 min	15 min	20 min	30 min	45 min	Study Report Location
[redacted] #2468/04	Zocor (Simvastatin) Lot #N5746	80 mg Tablet	Apparatus 2 Rotation: 50 rpm Medium: 0.5% SDS; pH 7.0 Volume: 900 mL Temperature: 37°C	12	48.2 (36.9-55.0)	83.3 (78.7-86.5)	91.7 (89.8-93.0)	95.2 (94.5-96.5)	97.1 (96.2-97.9)	Module 1, Section 3.9 p. 16

Therefore, it was recommended developing a dissolution method for ODT in the filing letter issued by the Agency and the following new method was submitted on May 15, 2006 through e-mail.

Dissolution medium: 0.15 % SDS buffer, pH 6.8
Stirring speed: 75 rpm
Vessel Volume: 900 ml
Temperature: 37±0.5°C
Sampling points: 3, 6, 10, 15, 20, 30, 45, and 60 minutes

Study results of the dissolution study based on the new method appeared to be acceptable (e.g., 80mg ODT, Figure 2). However, the results based on the new method must be formally submitted for the approval.

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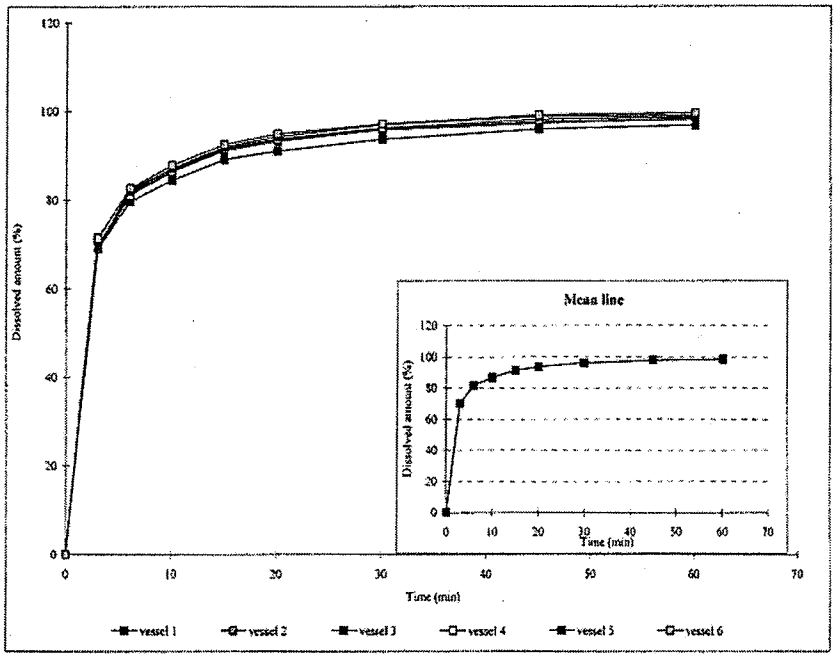
Dissolution profile 1 (0.15 % SDS) of SVT 80 mg ODT tablets [redacted] no. 2630/04, batch 3118403V3)



Dissolution results

Time (min)	vessel 1 (%)	vessel 2 (%)	vessel 3 (%)	vessel 4 (%)	vessel 5 (%)	vessel 6 (%)	MIN (%)	Average (%)	SD	RSD (%)
0	0.00	0.00	0.00	0.00	0.00	0.00	0.0	0.0	0.00	0.00
3	69.10	71.71	69.24	69.23	69.78	71.40	69.1	70.1	1.17	1.67
6	79.75	82.55	81.65	81.17	82.10	82.77	79.7	81.7	1.11	1.35
10	84.56	86.94	86.50	86.50	87.21	87.92	84.6	86.6	1.13	1.31
15	89.15	91.66	91.25	91.54	92.04	92.57	89.2	91.4	1.18	1.29
20	91.06	93.66	93.29	93.77	94.37	94.97	91.1	93.5	1.34	1.44
30	93.75	95.87	95.92	96.30	97.04	97.18	93.8	96.0	1.23	1.29
45	95.98	97.19	97.60	98.17	98.74	99.13	96.0	97.8	1.14	1.17
60	96.84	98.29	98.15	98.64	99.03	99.61	96.8	98.4	0.94	0.95

Figure 2 **Results of 80mg dissolution study using the new method**

The sponsor proposed the specification as Q > [redacted] The study results of the new method indicated that the specification should be Q [redacted] in 15 minutes. The sponsor accepted the revised specification through teleconference and e-mail response on May 17, 2006. The sponsor must concurrently validate the new dissolution method while performing the lot release testing using the original method according to the reviewing chemistry reviewer. In addition, the new method should be included in the stability protocol.

b(4)

3.3 Analytical

3.3.1 Is bioanalytical method acceptable?

Plasma concentrations of simvastatin and simvastatin acid were measured using standard HPLC/MS/MS. The report on bioanalytical method validation was summarized in Table 5, and the method was acceptable based on the results.

Table 6 Results of bioanalytical method validation

	Simvastatin	Simvastatin acid
Limit of quantitation (ng/ml)	0.5	0.1
Standard curve concentrations (ng/ml)	0.50-150.00	0.10-50.00
QC concentrations (ng/ml)	0.50, 1.50, 10.00, 75.00, 100.00, 150.00	0.30, 25.00, and 50.00
QC intraday precision range (%)	1.0-9.0	0.6-8.3
QC intraday accuracy range (%)	95.5-103.1	95.7-103.9
QC interday precision range (%)	0.7-2.1	0.6-14.9
QC interday accuracy range (%)	95.5-103.4	97.4-101.8

There were numerous unacceptable compliance issues from the study sites according the results of DSI inspection, and it was concluded that the study was not acceptable to DSI. It indicates that the pharmacokinetic data are not reliable to evaluate BE of ODT.

4 Labeling Comments

N/A

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/s/

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5/19/2006 08:39:54 AM
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