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RESEARCH**

*APPLICATION NUMBER:*

**206679Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

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<b>NDA</b>	206-679 Serials 000; 003; 0011
<b>Submission Dates</b>	June 22, 2015; October 6, 2015; February 26, 2016
<b>Brand Name</b>	Not determined
<b>Generic Name</b>	Simvastatin
<b>Reviewer</b>	S.W. Johnny Lau, R.Ph., Ph.D.
<b>Team Leader</b>	Jayabharathi Vaidyanathan, Ph.D.
<b>OCP Division</b>	Clinical Pharmacology 2
<b>OND Division</b>	Metabolism and Endocrinology Products
<b>Sponsor</b>	Perrigo Pharmaceuticals
<b>Formulation; Strength</b>	Suspension; 40 mg/5 mL and 20 mg/5 mL
<b>Indication</b>	Adjunct therapy to diet to reduce elevated lipid concentrations

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### **1 Executive Summary**

The sponsor seeks approval of the 40 mg/5 mL and 20 mg/5 mL simvastatin oral suspension as an adjunct therapy to reduce elevated lipid concentrations via the regulatory 505(b)(2) pathway. The innovator 10, 20, 40, and 80 mg simvastatin tablets (Zocor) have the indication to treat hyperlipidemia (NDA 19-766 approved on December 23, 1991).

#### **1.1 Recommendations**

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 206-679's Clinical Pharmacology data submitted on June 22, 2015, October 6, 2015, and February 26, 2016. The data are acceptable to support approval. Due to the significant effect of food on the exposure of simvastatin suspension, the product label needs to carry the following statement:

- The recommended usual starting dose is 10 or 20 mg once a day in the evening on an empty stomach.

## 1.2 Post Marketing Requirement

Not applicable.

## 1.3 Summary of Important Clinical Pharmacology Findings

The sponsor submitted the results of 3 clinical pharmacology studies (PRG-NY-14-010, PRG-NY-14-011, and SC02806) to support NDA 206-679. Study PRG-NY-14-010 assessed the bioequivalence between 80 mg simvastatin oral suspension (10 mL of 40 mg/5mL) and 80 mg simvastatin tablet (Zocor) under fasting. Study PRG-NY-14-011 assessed the relative bioavailability of 80 mg simvastatin suspension (10 mL of 40 mg/5mL) in the presence of a high fat meal and under fasting. Study SC02806 assessed the relative bioavailability between 20 mg simvastatin oral suspension (20 mg/5 mL) and 20 mg Zocor tablet under fasting. The sponsor requested a biowaiver for the 20 mg/5 mL simvastatin oral suspension. See Biopharmaceutics reviewer's review for the request of biowaiver.

Results of simvastatin  $C_{max}$  and AUCs indicate that 10 mL of 40 mg/5 mL simvastatin oral suspension is bioequivalent to the 80 mg simvastatin tablet (Zocor) under fasting via the reference scaled bioequivalence approach. Results of simvastatin acid  $C_{max}$  indicate that 10 mL of 40 mg/5 mL simvastatin oral suspension is not equivalent to the 80 mg simvastatin tablet (Zocor) under fasting via the reference scaled bioequivalence approach. However, results of simvastatin acid AUCs indicate that 10 mL of 40 mg/5 mL simvastatin oral suspension is equivalent to the 80 mg simvastatin tablet (Zocor) under fasting condition via the reference scaled bioequivalence approach. Simvastatin (parent drug) pharmacokinetic data are primary to assess bioequivalence between simvastatin suspension and 80 mg Zocor tablet, whereas simvastatin acid (metabolite) pharmacokinetic data are considered supportive evidence.

The submission batches for the simvastatin suspension were manufactured at full scale-up (commercial) size. There are no differences between the formulation of the submission batches, clinical batch, and proposed commercial formulation. The 80 mg Zocor tablets used in Study PRG-NY-14-010 is the United States-approved and marketed product. Also, the Orange Book lists 80 mg Zocor as the reference listed drug.

Study PRG-NY-14-011 shows that a high fat meal affects the exposure of simvastatin suspension. Simvastatin  $C_{max}$  geometric mean ratio under fed and fasting conditions as well as that of simvastatin  $AUC_{0-\infty}$  decreased 26.4% and 17.5%, respectively. Simvastatin acid  $C_{max}$  geometric mean ratio under fed and fasting conditions as well as that of simvastatin acid  $AUC_{0-\infty}$  increased 73.2% and 43.8%, respectively.

## 2 Question-Based Review

### 2.1 Background

The sponsor is developing the oral 40 mg/5 mL and 20 mg/5 mL simvastatin suspension to treat hypercholesterolemia via the regulatory 505(b)(2) pathway. The innovator 10, 20, 40, and 80 mg simvastatin tablets have the indication to treat hypercholesterolemia.

The sponsor conducted the following 3 studies to support NDA 206-679:

- PRG-NY-14-010: Bioequivalence between 80 mg simvastatin oral suspension (10 mL of 40 mg/5mL) and 80 mg simvastatin tablet (Zocor) under fasting
- PRG-NY-14-011: Relative bioavailability of 80 mg simvastatin suspension (10 mL of 40 mg/5mL) in the presence of a high fat meal and under fasting
- SC02806: Relative bioavailability study between 20 mg/5 mL of simvastatin suspension and 20 mg Zocor tablet

Because the 20 mg Zocor tablets used in Study SC02806 were the 20 mg Zocor marketed in the UK (Page 23 of 954 on Study SC02806's report) and not the United States reference listed drug, this reviewer did not review Study SC02806 for the support of NDA 206-679.

Besides simvastatin's product label, the following publication details simvastatin's clinical pharmacology:

- Neuvonen P et al. Pharmacokinetic comparison of the potential over-the-counter statins simvastatin, lovastatin, fluvastatin and pravastatin. *Clin Pharmacokinet* 2008;47:565463-74.

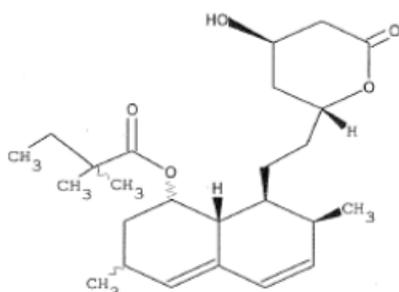
For simplicity, this reviewer refers the simvastatin metabolite,  $\beta$ -hydroxyacid simvastatin, as simvastatin acid in this review.

### 2.2 General Attributes

#### 2.2.1 What are simvastatin's key physicochemical properties?

Figure 1 shows the chemical structure of simvastatin, which has a molecular weight of 418.57 and empirical formula of  $C_{25}H_{38}O_5$ .

Figure 1. Simvastatin's molecular structure.



Source: Module 3.2.S.1.2

## 2.2.2 What is the formulation for the to-be-marketed simvastatin oral suspension?

Tables 1 and 2 detail the formulations of the to-be-marketed immediate release simvastatin oral suspension.

Table 1. Composition of the to-be-marketed simvastatin oral suspension 40 mg/5 mL.

Component	Compendial Quality	Function	mg/5 mL Dose	Formulation %w/w			
Simvastatin	USP	Active ingredient	40	0.8			
Propylene Glycol	USP	(b) (4)	(b) (4)	(b) (4)			
Methylparaben	NF						
Ethylparaben	NF						
Propylparaben	NF						
Magnesium Aluminum Silicate	NF						
Carboxymethylcellulose Sodium	NF						
Simethicone Emulsion	USP						
Sodium Lauryl Sulfate	NF						
Acesulfame Potassium	NF						
Citric Acid Monohydrate	USP						
Sodium Phosphate, Dibasic, Anhydrous	USP						
Strawberry Flavoring (b) (4)	NA				Flavor	(b) (4)	(b) (4)
(b) (4) Water	USP				(b) (4)	N/A	NA

NA = not applicable

\*Strawberry flavor contains (b) (4)% propylene glycol; specific amounts of the remaining ingredients are proprietary information.  
Source: Module 3.2.P.1.2 Table P.1.2-2

Table 2. Composition of the to-be-marketed simvastatin oral suspension 20 mg/5 mL.

Component	Compendial Quality	Function	mg/5 mL Dose	Formulation %w/w			
Simvastatin	USP	Active ingredient	20	0.4			
Propylene Glycol	USP	(b) (4)	(b) (4)	(b) (4)			
Methylparaben	NF						
Ethylparaben	NF						
Propylparaben	NF						
Magnesium Aluminum Silicate	NF						
Carboxymethylcellulose Sodium	NF						
Simethicone Emulsion	USP						
Sodium Lauryl Sulfate	NF						
Acesulfame Potassium	NF						
Citric Acid Monohydrate	USP						
Sodium Phosphate, Dibasic, Anhydrous	USP						
Strawberry Flavoring (b) (4)	NA				Flavor	(b) (4)	(b) (4)
(b) (4) Water	USP				(b) (4)	N/A	NA

NA = not applicable

\*Strawberry flavor contains (b) (4)% propylene glycol; specific amounts of the remaining ingredients are proprietary information.  
Source: Module 3.2.P.1.2 Table P.1.2-1

## 2.3 General Clinical Pharmacology

### 2.3.1 What are simvastatin's clinical pharmacokinetic (PK) characteristics?

The following is extracted from Neuvonen P et al. *Clin Pharmacokinet* 2008;47:565463-74.

Simvastatin is a lipophilic lactone prodrug, whereas other statins such as fluvastatin and pravastatin are given as active acid forms.

### **Bioavailability**

The oral bioavailability of simvastatin is low (< 5%), largely because its cytochrome P450 (CYP) 3A-mediated first-pass metabolism. The interindividual variation in the area under the plasma concentration-time curve (AUC) of simvastatin is about (b) (4). Simvastatin acid, a metabolite, is a substrate of P-glycoprotein. The interplay of CYP3A4 and P-glycoprotein in the intestinal wall may contribute to the high presystemic extraction of simvastatin. Simvastatin is also a substrate of other efflux or uptake transporters. The activity of CYP3A and transporter proteins, as well as the contents and pH of the gastrointestinal tract can affect the bioavailability of simvastatin.

### **Protein Binding and Elimination**

Protein binding of the lipophilic simvastatin in plasma is high (> 95%). The elimination half-life of simvastatin is (b) (4) hours. This short elimination half-life explains its better cholesterol-lowering efficacy when taken in the evening because steroid synthesis is more active during the night.

### **Metabolism**

Simvastatin shows extensive metabolism via CYP3A. The parent simvastatin lactone is either oxidized by CYP3A4 (and CYP3A5) in the intestinal wall and liver to several metabolites, or hydrolyzed to their active open acids (simvastatin acid). Simvastatin acid is further metabolized by CYP3A and CYP2C8.

### **Hepatic Transport Mechanisms**

Hepatocytes are the site of therapeutic action for simvastatin. Simvastatin is a substrate of the organic anion transporting polypeptide (OATP) 1B1. Other hepatic uptake transporters that can transport simvastatin are OATP1B3, OATP2B1, and OATP1A2. For lipophilic statins, the concentrations that cause a 50% reduction (IC<sub>50</sub> values) in HMG-CoA reductase activity are of the same magnitude in both nonhepatic and hepatic cell-based assays.

Liver primarily clears simvastatin via active hepatic uptake, metabolism, and biliary excretion. Efflux transporters localized on the canalicular membrane of the hepatocyte, such as P-glycoprotein, multidrug resistance-associated protein (MRP)2, breast cancer resistance protein (BCRP), and bile salt export pump (BSEP) can be the final step to transport simvastatin from the portal circulation into bile. Alterations in the function of these hepatic transporters may decrease simvastatin elimination.

#### **2.3.2 What is the relative bioavailability between 80 mg simvastatin suspension (10 mL of 40 mg/5 mL) and 80 mg simvastatin tablet (innovator US approved product)?**

Study PRG-NY-14-010 was a 2-treatment, 3-period, 3-way crossover study in healthy men of 20 – 41 years (mean age 30.5 years), a weight range of 50 – 95 kg (mean: 73.6 kg), a height range of 151 – 183 cm (mean: 165.7 cm) and Body Mass Index (BMI) range of 19 – 29.9 kg/m<sup>2</sup> (mean: 26.8 kg/m<sup>2</sup>).

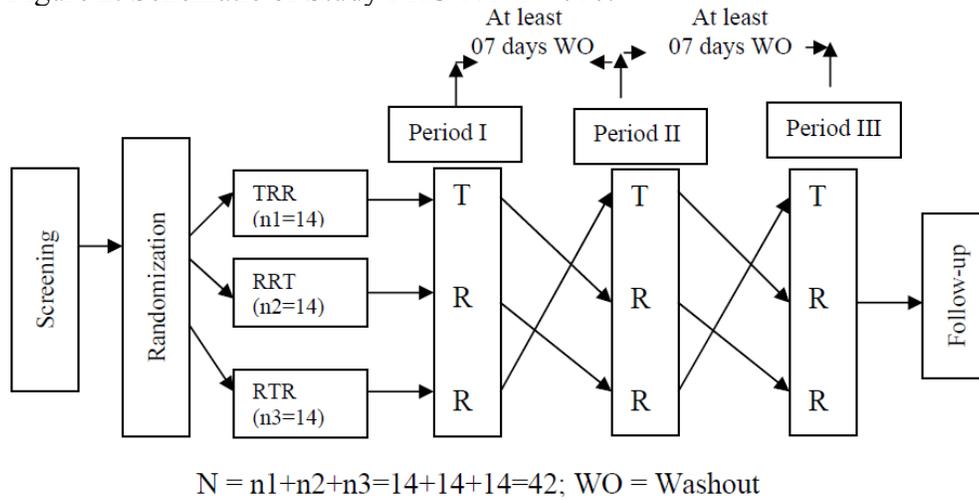
Each randomized participant orally received an 80 mg simvastatin dose in the following 3 treatments after a fast for at least 10 hours:

- 10 mL of 40 mg/5 mL simvastatin oral suspension (test)
- an 80 mg ZOCOR oral tablet (reference)
- an 80 mg ZOCOR oral tablet (reference)

Participants received each treatment with 240 mL ambient temperature water and fasted for 4 hours postdose. A washout of at least 7 days separated each treatment. The sponsor collected serial plasma samples predose and 32 hours postdose to determine simvastatin and simvastatin acid concentrations via a

validated bioanalytical method. Figure 2 shows the schematic of Study PRG-NY-14-010.

Figure 2. Schematic of Study PRG-NY-14-010.



The sponsor prospectively designed Study PRG-NY-14-010 via the reference scaled bioequivalence approach. If the 90% confidence intervals (CIs) of the ratio estimates for  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  were within 80.00 to 125.00%, then the Test treatment would be concluded as bioequivalent to the Reference treatment.

For any log-transformed pharmacokinetic parameter, where the within-subject variability of the Reference product ( $\sigma_{WR}$ ) was at least 0.294, bioequivalence was to be evaluated via the Scaled Average Bioequivalence approach. Through this approach, the 95% upper confidence bounds of the Reference-scaled criterion were computed.

Scaled Average Bioequivalence for the log-transformed pharmacokinetic parameters was evaluated via testing the following null hypothesis:

$$H_0: (\mu_T - \mu_R)^2 / \sigma_{WR}^2 > \theta$$

Versus the alternative hypothesis

$$H_1: (\mu_T - \mu_R)^2 / \sigma_{WR}^2 \leq \theta$$

where  $\mu_T$  and  $\mu_R$  were the averages of the log-transformed pharmacokinetic parameters  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  for the Test and Reference products, respectively;  $\theta$  was the Scaled Average Bioequivalence limit which was calculated via the following formula:

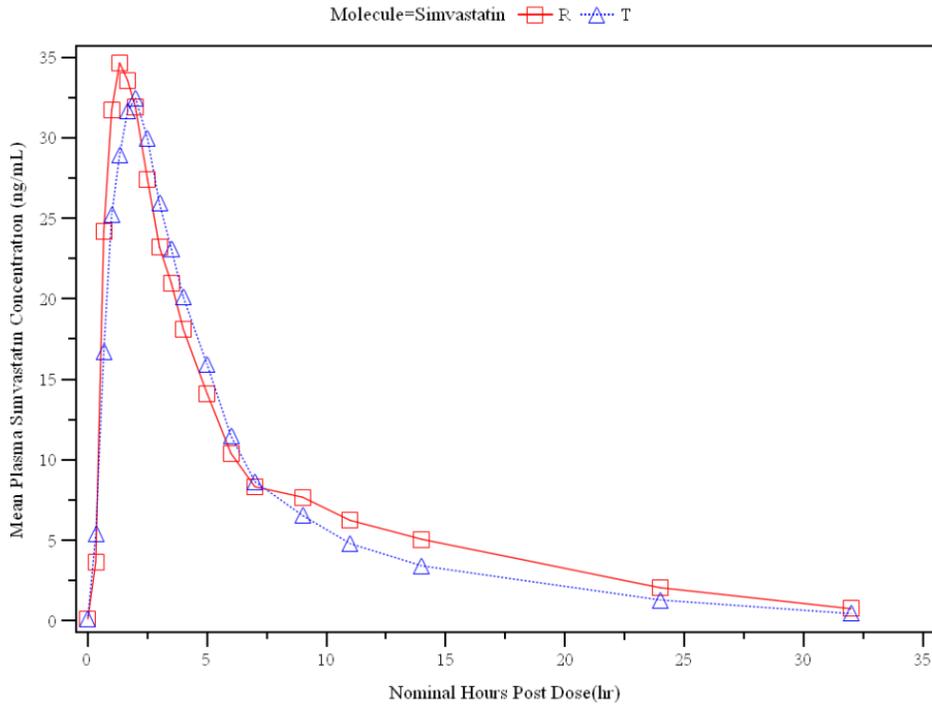
$$\theta = (\ln \Delta)^2 / \sigma_{WO}^2$$

Where  $\Delta$  was 1.25, the usual average BE upper limit for the untransformed Test/Reference ratio of geometric means, and  $\sigma_{WO}=0.25$ .

If the following 2 conditions were satisfied, then the Test Product would be considered bioequivalent to the Reference Product for the parameter:

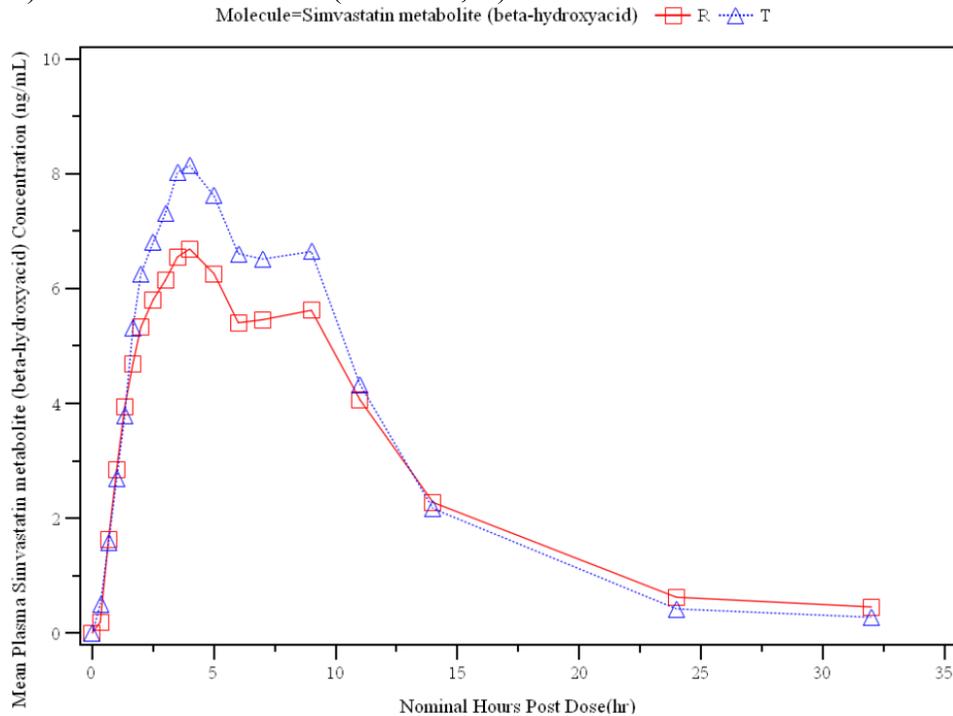
- The 95% upper confidence bound for  $(\mu_T - \mu_R)^2 / \sigma_{WR}^2 \leq \theta$ , or equivalently, the 95% upper confidence bound for  $(\mu_T - \mu_R)^2 - \theta * \sigma_{WR}^2 \leq 0$ .
- The point estimate of the Test/Reference geometric mean ratio falls within 80.00% to 125.00%.

Figure 3. Mean plasma simvastatin concentration-time profiles for the simvastatin suspension (test, T) and simvastatin tablet (reference, R).



Source: Study PRG-NY-14-010 study report Figure 14.2.1.1

Figure 4. Mean plasma simvastatin acid concentration-time profiles for the simvastatin suspension (test, T) and simvastatin tablet (reference, R).



Source: Study PRG-NY-14-010 study report Figure 14.2.1.5

Table 3. Simvastatin pharmacokinetic parameters for the simvastatin suspension (test) and simvastatin tablet (reference).

Summary Statistics	Simvastatin						
	C <sub>max</sub> (ng/mL)	AUC <sub>0-t</sub> (ng hr/mL)	AUC <sub>0-∞</sub> (ng.hr/mL)	T <sub>max</sub> (Hour)	t <sub>1/2</sub> (Hour)	K <sub>el</sub> (1/hr)	AUC <sub>Ratio</sub> (%)
<b>Treatment T (Test): (N=36)</b>							
Mean (SD)*	43.754 (22.9946)	204.619 (93.2194)	210.012 (93.7379)	2.00	6.404 (1.4727)	0.114 (0.0275)	97.06 (2.248)
GM	38.103	186.647	192.347	1.80	6.242	0.111	97.04
(Min, Max)	(10.319, 97.528)	(83.232, 509.584)	(86.463, 518.483)	(0.67, 5.00)	(3.343, 10.609)	(0.065, 0.207)	(87.37, 99.17)
%CV	52.55	45.56	44.63	42.90	23.00	24.10	2.32
<b>Treatment R (Reference): (N=76)</b>							
Mean (SD)*	54.711 (36.1474)	227.356 (103.0450)	235.795 (105.2573)	1.33	6.870 (1.7762)	0.107 (0.0240)	96.25 (3.053)
GM	45.734	210.143	218.442	1.43	6.672	0.104	96.20
(Min, Max)	(13.217, 213.902)	(109.887, 689.229)	(113.171, 716.343)	(0.67, 5.00)	(4.404, 13.110)	(0.053, 0.157)	(84.75, 99.53)
%CV	66.07	45.32	44.64	55.28	25.85	22.49	3.17

Source: Modified from Study PRG-NY-14-010 study report Table 11.4-1(A)

Table 4. Simvastatin acid pharmacokinetic parameters for the simvastatin suspension (test) and simvastatin tablet (reference).

Summary Statistics	Simvastatin Metabolite (beta-hydroxyacid)						
	C <sub>max</sub> (ng/mL)	AUC <sub>0-t</sub> (ng hr/mL)	AUC <sub>0-∞</sub> (ng.hr/mL)	T <sub>max</sub> (Hour)	t <sub>1/2</sub> (Hour)	K <sub>el</sub> (1/hr)	AUC <sub>Ratio</sub> (%)
<b>Treatment T (Test): [N=36]</b>							
Mean (SD)*	9.790 (5.4606)	91.451 (48.5137)	93.928 (49.0385)	4.00	5.114 (1.6734)	0.147 (0.0421)	97.29 (2.820)
GM	8.713	82.187	84.516	4.24	4.898	0.142	97.24
(Min, Max)	(4.036, 25.829)	(36.268, 250.857)	(36.953, 252.543)	(1.00, 9.00)	(2.393, 11.886)	(0.058, 0.290)	(86.85, 99.61)
%CV	55.78	53.05	52.21	45.17	32.72	28.59	2.90
<b>Treatment R (Reference): [N=76]</b>							
Mean (SD)*	7.781 (3.7950)	84.384 (44.8179)	89.405 (47.4748)	4.00	6.568 (2.1313)	0.116 (0.0368)	94.45 (5.061)
GM	7.015	75.826	80.407	3.83	6.258	0.111	94.30
(Min, Max)	(3.130, 20.781)	(34.839, 260.923)	(35.296, 293.759)	(0.67, 9.00)	(2.779, 14.997)	(0.046, 0.249)	(73.86, 99.64)
%CV	48.77	53.11	53.10	57.22	32.45	31.69	5.36

Source: Modified from Study PRG-NY-14-010 study report Table 11.41(B)

Table 5. Statistical analysis of simvastatin pharmacokinetic parameters of 80 mg simvastatin suspension (test) to 80 mg simvastatin tablet (reference).

PK Parameter	Least Squares Geometric Means of Treatment:		Ratio (%)	Intra-subject %CV	90% CI of Ratio
	Test (T) N=36	Reference (R) N=38			
<b>C<sub>max</sub> (ng/mL)</b>	38.8401	45.2347	<b>85.86</b>	37.14	<b>(75.97 , 97.05)</b>
<b>AUC<sub>0-t</sub> (ng hr/mL)</b>	189.5880	210.5749	90.03	27.79	(82.05 , 98.79)
<b>AUC<sub>0-∞</sub> (ng hr/mL)</b>	195.1368	218.9752	89.11	28.13	(81.13 , 97.89)

Source: Study PRG-NY-14-010 study report Table 11.4-3

Table 6. Reference scaled approach to assess bioequivalence of simvastatin between 80 mg simvastatin suspension (test) and 80 mg simvastatin tablet (reference).

Parameters (Simvastatin)	Reference Variability (swr)	95% Upper Bound
<b>C<sub>max</sub> (ng/mL)</b>	0.3684899	-0.023961

Source: Study PRG-NY-14-010 study report Table 11.4-4

Table 7. Statistical analysis of simvastatin acid pharmacokinetic parameters of 80 mg simvastatin suspension (test) to 80 mg simvastatin tablet (reference).

PK Parameter	Least Squares Geometric Means of Treatment:		Ratio (%)	Intra-subject %CV	90% CI of Ratio
	Test (T) N=36	Reference (R) N=38			
<b>C<sub>max</sub> (ng/mL)</b>	8.6543	6.9238	<b>124.99</b>	30.33	<b>(112.98 , 138.28)</b>
<b>AUC<sub>0-t</sub> (ng hr/mL)</b>	81.2358	75.1157	108.15	27.13	(98.76 , 118.42)
<b>AUC<sub>0-∞</sub> (ng hr/mL)</b>	83.4556	79.7169	104.69	27.86	(95.38 , 114.91)

Source: Study PRG-NY-14-010 study report Table 11.4-5

Table 8. Reference scaled approach to assess bioequivalence of simvastatin acid between 80 mg simvastatin suspension (test) and 80 mg simvastatin tablet (reference).

Parameters (Simvastatin Acid)	Reference Variability (swr)	95% Upper Bound
<b>C<sub>max</sub> (ng/mL)</b>	0.3009861	0.0369822

Source: Study PRG-NY-14-010 study report Table 11.4-6

The sponsor stated the following for the test and reference treatments:

- “There are no differences between the formulation of the submission batches, clinical batch, and proposed commercial formulation.” (Page 28 of 82 in the Drug Product Summary (Section 2.3.P)).
- “The submission batches were manufactured at full scale-up (commercial) size. All process parameters used for the submission batches are the same as those proposed for use in commercial production.” (Product Quality Summary, Section 2.3.P, Page 35 of 82).
- The sponsor confirmed on the February 26, 2016 that the simvastatin tablet lot number J008788 used in Study PRG-NY-14-010 is the same product approved in the United States and marketed as 80 mg Zocor® tablets under Merck’s NDA 19-766.

Study PRG-NY-14-010's report (Page 30/589) states that "The sponsor supplied the investigational products. These materials were placed in the control of a qualified pharmacist at (b) (4) for receipt, storage, dispensing as per the randomization schedule created by (b) (4) biostatistician using SAS® 9.2 Enterprise Guide 4.2, and for subsequent retention after completion of the study, along with necessary documents for the purpose." Study PRG-NY-14-010's report also cites the sponsor's SOP No:22/81 for the receipt, storage, dispensing retention and dispatch of investigational products as well as the web address for the reference of 21CFR320.38 and 21CFR320.63 for the retention of bioavailability/bioequivalence samples.

### **Reviewer's Comments**

NDA 206-679 does not have an associated IND submission. However, the Division of Metabolism and Endocrinology Products (DMEP) granted the sponsor's pre-NDA submission meeting request (February 24, 2014) via correspondence. The meeting package contained the bioequivalence study protocol PRG-NY-14-010. OND QA Biopharmaceutics group reviewed Protocol PRG-NY-14-010 because OND QA Biopharmaceutics group reviewed bioequivalence studies and protocols at that time period. See meeting minutes dated March 21, 2014 in DARRTS.

The sponsor prospectively used reference scaled bioequivalence approach to assess bioequivalence between simvastatin suspension (test) and simvastatin tablet (reference) in the pivotal bioequivalence study. The Office of Clinical Pharmacology previously used the regular 2 one-sided tests procedure to assess simvastatin containing fixed dose combination tablets (Vytorin [NDA 21-687], Simcor [NDA 22-078], and Juvisync [NDA 202-343]). The Office of Generic Drugs published product specific guidances for simvastatin tablets and simvastatin orally disintegrating tablets. These guidances recommend the use of the regular 2 one-sided tests procedure to assess simvastatin bioequivalence, whereas the reference scaled bioequivalence approach is used to assess bioequivalence of generic drugs such as progesterone.

This reviewer's statistical analyses results are consistent with the sponsor's analyses. This reviewer used the SAS codes for reference scaled bioequivalence approach recommended by the "Draft Guidance on Progesterone" to assess the bioequivalence between simvastatin suspension and simvastatin tablet (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm209294.pdf>). This reviewer observed only slight differences after the decimal point for the following:

- estimated GMR ratios and 90% CI for simvastatin  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  (Table 5)
- Reference Variability (swr) and 95% Upper Bound for simvastatin  $C_{max}$  (Table 6)
- estimated GMR ratios and 90% CI for simvastatin acid  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  (Table 7)
- Reference Variability (swr) and 95% Upper Bound for simvastatin acid  $C_{max}$  (Table 8)

This reviewer's estimated the Reference Variability (swr) for simvastatin  $AUC_{0-t}$  and  $AUC_{0-\infty}$  is 0.2743289733 and 0.2721163008, respectively. Because these estimated values are less than 0.294, the 2 one-sided tests procedure to determine bioequivalence for simvastatin  $AUC_{0-t}$  and  $AUC_{0-\infty}$  is valid as used by the sponsor. Also, this reviewer's estimated the Reference Variability (swr) for simvastatin acid  $AUC_{0-t}$  and  $AUC_{0-\infty}$  is 0.2617861203 and 0.2609779863, respectively. Because these estimated values are less than 0.294, the 2 one-sided tests procedure to determine bioequivalence for simvastatin acid  $AUC_{0-t}$  and  $AUC_{0-\infty}$  is valid as used by the sponsor.

Because the 95% upper bound of simvastatin  $C_{max}$  is -0.023961 ( $\leq 0$ ) and the ratio of test/reference geometric mean ratio is within 80 – 125% (85.86%) as well as the 90% confidence intervals for simvastatin  $AUC_{0-t}$  and  $AUC_{0-\infty}$  are within 80 – 125%, the test simvastatin suspension is bioequivalent to the reference 80 mg Zocor tablets under fasting.

The 95% upper bound of simvastatin acid  $C_{\max}$  is 0.0369822 ( $> 0$ ), the reference scaled bioequivalence approach did not show equivalence between the simvastatin acid  $C_{\max}$  of test simvastatin suspension and the simvastatin acid  $C_{\max}$  of reference 80 mg Zocor tablets under fasting. This may be acceptable for the assessment of bioequivalence between simvastatin suspension and 80 mg Zocor tablet because:

- The Bioavailability and Bioequivalence guidance recommends the parent drug to be analyzed via the confidence interval approach, whereas metabolite data are for supportive evidence (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM389370.pdf>).
- The Office of Generic Drugs uses the simvastatin data to assess bioequivalence, whereas the simvastatin acid data are for supportive evidence (<http://www.fda.gov/downloads/drugs/guidancecomplianceinformation/guidances/ucm089636.pdf>).
- The Zocor label recommends dose adjustment for simvastatin when there is significant increase in both simvastatin and simvastatin acid exposures. Hence, the 25% higher simvastatin acid  $C_{\max}$  observed in Study PRG-NY-010 may not pose a safety concern.

### 2.3.3 How does food affect the bioavailability of 80 mg simvastatin suspension (10 mL of 40 mg/5 mL)?

Study PRG-NY-14-011 assessed the effect of food on the bioavailability of 80 mg simvastatin suspension. This was a 2-treatment, 2-period, 2-sequence, and crossover study in healthy men and women of 18 – 44 years (mean: 29.3 years), a weight range of 52 – 83.1 kg (mean: 68.3 kg), a height range of 153.5 – 182 cm (mean: 167.4 cm) and BMI range of 19 – 28.9 kg/m<sup>2</sup> (mean: 24.4 kg/m<sup>2</sup>). Each randomized participant orally received the following 2 treatments:

- 10 mL of 40 mg/5 mL simvastatin oral suspension after a high fat meal
- 10 mL of 40 mg/5 mL simvastatin oral suspension after at least a 10 hours fast

Participants received each treatment with 240 mL ambient temperature water and fasted for at least 4 hours postdose. A washout of at least 7 days separated each treatment. The sponsor collected serial plasma samples predose and 32 hours postdose to determine simvastatin and simvastatin acid concentrations via validated bioanalytical method. Figure 5 shows the schematic of Study PRG-NY-14-011.

Figure 5. Schematic of Study PRG-NY-14-011.

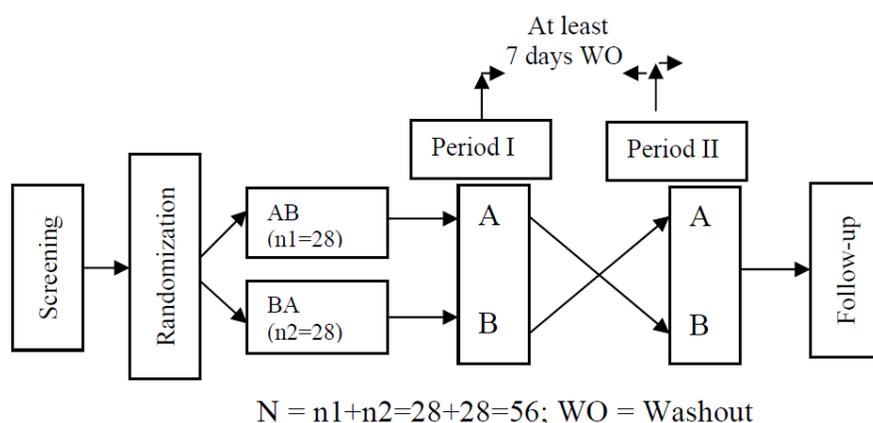


Figure 6 shows the mean plasma simvastatin concentration-time profiles under fed and fasting conditions. Figure 7 shows the mean plasma simvastatin acid concentration-time profiles under fed and fasting conditions.

Figure 6. Mean plasma simvastatin concentration-time profiles for 80 mg simvastatin suspension under fed (A) and fasting (B) conditions.

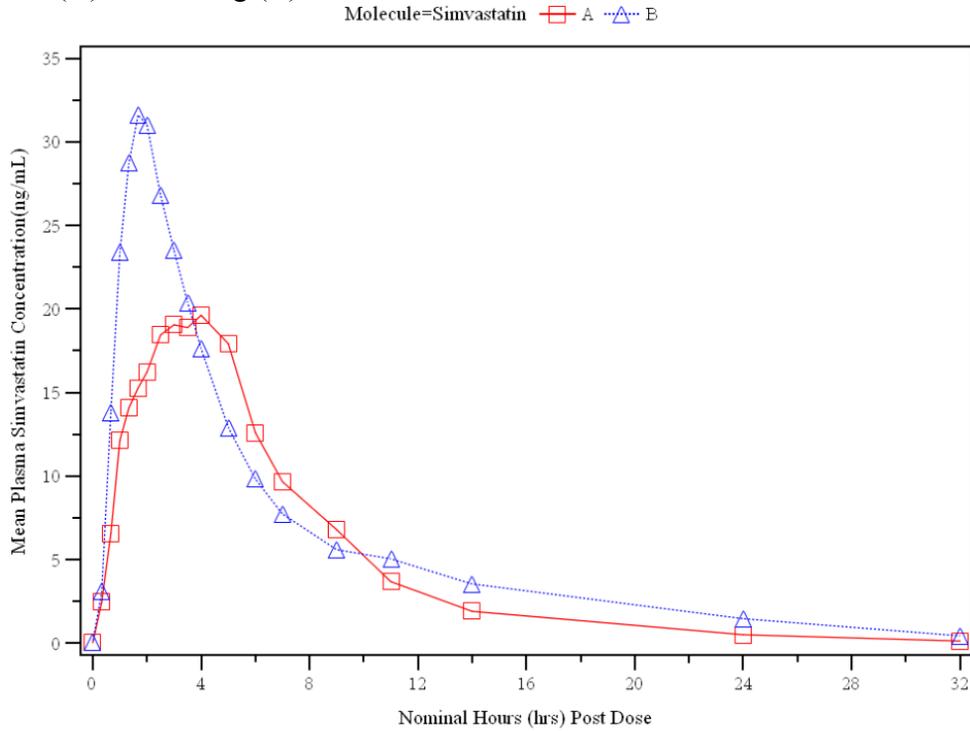


Figure 7. Mean plasma simvastatin acid concentration-time profiles for 80 mg simvastatin suspension under fed (A) and fasting (B) conditions.

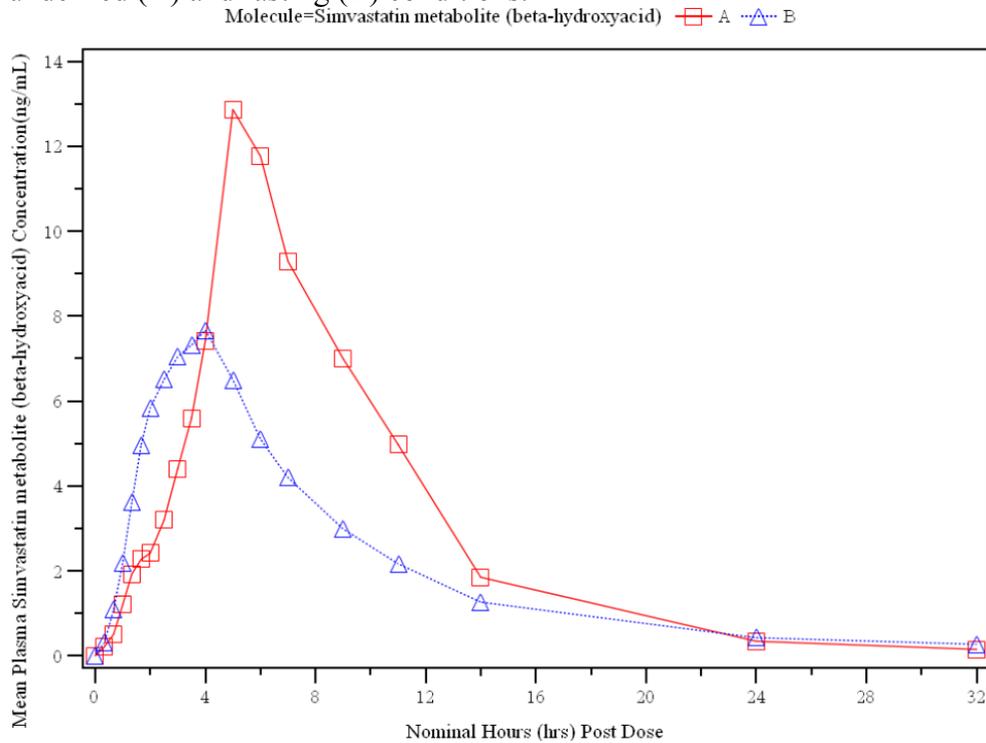


Table 9. Simvastatin pharmacokinetic parameters of 80 mg simvastatin suspension under fed and fasting conditions.

Summary Statistics	Simvastatin						
	C <sub>max</sub> (ng/mL)	AUC <sub>0-t</sub> (ng hr/mL)	AUC <sub>0-∞</sub> (ng.hr/mL)	T <sub>max</sub> (Hour)	t <sub>1/2</sub> (Hour)	K <sub>el</sub> (1/hr)	AUC_Ratio (%)
<b>Test Treatment (Fed state): (N=52)</b>							
Mean (SD)*	26.938 (14.5492)	150.375 (82.2938)	153.027 (82.5022)	3.50	4.667 (1.4636)	0.169 (0.0689)	97.86 (1.157)
GM	23.522	130.802	133.676	3.10	4.406	0.157	97.85
(Min, Max)	(6.154, 64.438)	(32.270, 379.706)	(33.660, 382.482)	(0.67, 9.00)	(2.010, 7.190)	(0.096, 0.345)	(94.64, 99.47)
%CV	54.01	54.73	53.91	47.25	31.36	40.87	1.18
<b>Reference Treatment (Fasting state): (N=52)</b>							
Mean (SD)*	38.872 (26.0720)	190.284 (130.5032)	196.627 (133.3935)	1.67	6.414 (2.1517)	0.121 (0.0441)	96.45 (2.774)
GM	32.003	155.686	161.484	1.69	6.076	0.114	96.41
(Min, Max)	(7.863, 115.369)	(34.950, 623.698)	(37.300, 640.847)	(0.67, 5.00)	(2.439, 12.854)	(0.054, 0.284)	(87.92, 99.64)
%CV	67.07	68.58	67.84	43.94	33.54	36.48	2.88

Source: Modified from Study PRG-NY-14-011 study report Table 11.4-1 (A)

Table 10. Simvastatin acid pharmacokinetic parameters of 80 mg simvastatin suspension under fed and fasting conditions.

Summary Statistics	Simvastatin Metabolite (beta-hydroxyacid)						
	C <sub>max</sub> (ng/mL)	AUC <sub>0-t</sub> (ng hr/mL)	AUC <sub>0-∞</sub> (ng.hr/mL)	T <sub>max</sub> (Hour)	t <sub>1/2</sub> (Hour)	K <sub>el</sub> (1/hr)	AUC_Ratio (%)
<b>Test Treatment (Fed state): (N=52)</b>							
Mean (SD)*	14.600 (7.7785)	95.695 (50.6424)	96.943 (51.3847)	5.50	4.001 (1.3095)	0.193 (0.0699)	98.73 (1.206)
GM	12.723	84.997	86.099	5.71	3.800	0.182	98.72
(Min, Max)	(3.446, 39.777)	(25.594, 308.672)	(26.089, 315.224)	(4.00, 9.00)	(1.536, 8.594)	(0.081, 0.451)	(92.66, 99.78)
%CV	53.28	52.92	53.01	19.89	32.73	36.24	1.22
<b>Reference Treatment (Fasting state): (N=52)</b>							
Mean (SD)*	8.494 (5.1502)	65.097 (36.5048)	68.669 (39.1279)	4.00	6.569 (3.5356)	0.134 (0.0622)	95.30 (5.096)
GM	7.337	56.877	59.774	3.46	5.804	0.119	95.15
(Min, Max)	(1.560, 32.143)	(19.205, 200.064)	(20.005, 211.414)	(1.33, 7.00)	(2.405, 19.405)	(0.036, 0.288)	(77.92, 99.63)
%CV	60.63	56.08	56.98	32.45	53.82	46.50	5.35

Source: Modified from Study PRG-NY-14-011 study report Table 11.4-1 (B)

Table 11. Statistical analysis of simvastatin pharmacokinetic parameters of 80 mg simvastatin suspension under fed (test) and fasting (reference) conditions (N=52).

PK Parameter	Least Squares Geometric Means of Treatment:		Ratio (%)	Intra-subject %CV	90% CI of Ratio
	Test Treatment (Fed State)	Reference Treatment (Fasting State)			
C <sub>max</sub> (ng/mL)	23.4610	31.8528	73.65	45.16	(63.92 , 84.87)
AUC <sub>0-t</sub> (ng hr/mL)	130.4119	155.6543	83.78	27.18	(76.74 , 91.47)
AUC <sub>0-∞</sub> (ng.hr/mL)	133.2920	161.4601	82.55	27.05	(75.65 , 90.09)

Source: Study PRG-NY-14-011 study report Table 11.4-3 (A)

Table 12. Statistical analysis of simvastatin acid pharmacokinetic parameters of 80 mg simvastatin suspension under fed (test) and fasting (reference) conditions (N=52).

PK Parameter	Least Squares Geometric Means of Treatment:		Ratio (%)	Intra-subject %CV	90% CI of Ratio
	Test Treatment (Fed State)	Reference Treatment (Fasting State)			
$C_{max}$ (ng/mL)	12.7211	7.3432	<b>173.24</b>	44.69	<b>(150.55 , 199.34)</b>
$AUC_{0-t}$ (ng hr/mL)	84.8878	56.9066	<b>149.17</b>	28.02	<b>(136.27 , 163.29)</b>
$AUC_{0-\infty}$ (ng hr/mL)	85.9925	59.8175	<b>143.76</b>	29.13	<b>(130.88 , 157.90)</b>

Source: Study PRG-NY-14-011 study report Table 11.4-3 (B)

Simvastatin  $C_{max}$  geometric mean ratio under fed and fasting conditions as well as that of simvastatin  $AUC_{0-\infty}$  decreased 26.4% and 17.5%, respectively, for the 80 mg simvastatin suspension. The 90% CI of the ratios of fed to fasting simvastatin  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  are not within the 80 – 125% bioequivalence goalpost.

Simvastatin acid  $C_{max}$  geometric mean ratio under fed and fasting conditions as well as that of simvastatin acid  $AUC_{0-\infty}$  increased 73.2% and 43.8%, respectively, for the 80 mg simvastatin suspension. The 90% CI of the ratios of fed to fasting simvastatin acid  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  are not within the 80 – 125% bioequivalence goalpost.

### Reviewer’s Comments

This reviewer’s statistical analyses results are consistent with the sponsor’s analyses. This reviewer used the SAS PROC GLM procedure to calculate the GMR and confidence interval (CI). This reviewer observed only slight differences after the decimal point for the estimated GMR and 90% CI but these differences do not alter the results’ interpretation.

Study PRG-NY-14-011 has the following issues:

- The sponsor did not use the food effect guidance recommended high fat meal. The Guidance recommends a high-fat (50% of total caloric meal content) meal of 800 – 1000 calories, where 150, 250, and 500 – 600 calories are from protein, carbohydrate, and fat, respectively. Table 13 shows that the caloric content of the meal used in Study PRG-NY-14-011 is consistent with the food effect guidance’s recommendation and thus Study PRG-NY-14-011’s high-fat meal is acceptable.

Table 13. Composition of the non-standard breakfast meal used in Study PRG-NY-14-011

Ingredients	Amount (g)	Energy (kcal)	Protein (kcal)	Fat (kcal)	Carbohydrate (kcal)
Whole Milk	240ml	227.49	26.36	150.57	50.56
Hash brown potatoes with 5 gm butter	90g	313.58	10.32	196.02	107.24
Chicken tikka	75g	191.52	89.92	100.08	1.52
Bread sliced with 20 gms butter	60g	187.44	21.20	70.92	95.32
Egg omelette	20g	34.31	10.96	22.59	0.76
<b>TOTAL</b>	<b>NA</b>	<b>954.34</b>	<b>158.76</b>	<b>540.18</b>	<b>255.4</b>
<b>PERCENTAGE</b>	<b>NA</b>	<b>NA</b>	<b>16.64</b>	<b>56.60</b>	<b>26.76</b>

Source: Study PRG-NY-14-011 Report Page 41 of 62

- This reviewer notices that the sponsor reported “kcal” as the unit for energy, protein, fats, and carbohydrate in Table 13, whereas the food effect guidance refers to “calories” as the unit for energy, protein, carbohydrate, and fat. The Calories on a food package are actually kilocalories (1000 calories = 1 kilocalorie) (<http://www.nutrition.gov/whats-food/commonly-asked-questions-faqs>). For example, a can of soda containing 200 Calories contains 200,000 calories, or 200 kilocalories.
- Table 14 shows the effect of food on the pharmacokinetic parameters of simvastatin and simvastatin acid when compared with fasting condition. Also, Table 14 compares the food effect on simvastatin suspension pharmacokinetic parameters with the food effect on the innovator simvastatin tablet as indicated on the innovator product (Zocor) label. Because the Zocor label does not specify the identities of the inhibitors, this reviewer finds it difficult to compare the food effect on simvastatin suspension with the food effect on the innovator product.

Table 14. Food effect on simvastatin suspension as compared to that under fasting.

Parameter	Geometric Mean Ratio of Parameter (fed vs. fasting) for Simvastatin Suspension	Innovator Simvastatin Tablet (Zocor) Food effect language on the product label
<b>Simvastatin</b>		
$C_{max}$	↓ 26.4%	Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.
$AUC_{0-t}$	↓ 16.2%	
$AUC_{0-\infty}$	↓ 17.5%	
<b>Simvastatin acid</b>		
$C_{max}$	↑ 73.2%	Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.
$AUC_{0-t}$	↑ 49.2%	
$AUC_{0-\infty}$	↑ 43.8%	

Source: Reviewer’s table

- This reviewer cannot find the caloric content of the “American Heart Association recommended low-fat meal” even with the help of the FDA librarian. Thus, this reviewer cannot verify whether the sponsor’s statement that a low fat meal has about 438 Kcal and 29% fat content (Page 26/26 of Section 2.7.1.3) refers to the “American Heart Association recommended low-fat meal” or not.
- Study PRG-NY-14-011 showed a 26.4 and 17.5% lower simvastatin  $C_{max}$  and simvastatin  $AUC_{0-\infty}$ , respectively, and a 73.2 and 43.8% higher simvastatin acid  $C_{max}$  and simvastatin acid  $AUC_{0-\infty}$ , respectively, after a high fat meal versus that under fasting.
- This reviewer contemplated the following options of recommendation:
  1. approval of this product without labeling recommendation
  2. approval of this product with label restriction to take simvastatin suspension in the evening on an empty stomach
  3. not approval but to show the bioequivalence of simvastatin suspension to the reference listed drug after a high fat meal

- Because the significant effect of food on the exposure of simvastatin suspension cannot be related to that of the label for the reference listed product and simvastatin suspension is a new dosage form, Option 1 may not be appropriate.
- Even though the simvastatin suspension is a new dosage form but on its own merit, Option 3 may not be appropriate because:
  - Niacin increases simvastatin  $C_{max}$  and AUC 8 and 40%, respectively, as well as increases simvastatin acid  $C_{max}$  and AUC 84 and 60%, respectively, without the need to adjust the dose of simvastatin per the Zocor label. Also, fenofibrate decreases simvastatin  $C_{max}$  and AUC 17 and 11%, respectively, as well as decreases simvastatin acid  $C_{max}$  and AUC 11 and 36%, respectively, without the need to adjust the dose of simvastatin per the Zocor label.
  - The Zocor label has cautionary statement on dosing simvastatin and niacin specific to Chinese. However, this caution for Chinese patients is not due to the pharmacokinetic interaction between niacin and simvastatin. Non-Chinese patients do not have restriction to use this combination of simvastatin and niacin. This cautionary restriction is due to the outcome trial which the increase in myopathy in Chinese was observed; the Zocor label also indicates that it is unknown if the risk applies to other patients.
- Thus, Option 2 seems to be the most appropriate recommendation for this submission.

## 2.4 Bioanalytical

### Are the bioanalytical methods properly validated to measure simvastatin and simvastatin acid in plasma samples?

The sponsor used a liquid chromatography with tandem mass spectrometry (LC/MS/MS) assay to determine the simvastatin and simvastatin acid concentrations in plasma samples. Table 15 details the validation of the bioanalytical assay.

Table 15. Validation of the bioanalytical assay to measure simvastatin and simvastatin acid in plasma samples for Studies PRG-NY-14-010 and PRG-NY-14-011.

Analyte	Simvastatin	Simvastatin Acid
Matrix	Plasma	Plasma
Anticoagulant	K <sub>2</sub> EDTA	K <sub>2</sub> EDTA
Sample volume, mL	0.3	0.3
Lower limit of quantitation, ng/mL	0.2	0.051
Linear range, ng/mL	0.2 – 50.01	0.051 – 15.2
Average recovery (%)	86.22	77.37
Assay precision (%CV of QC samples)		
Inter-batch	4.36 – 7.17	3.6 – 13.19
Intra-batch	0.27 – 10.19	0.84 – 17.88
Assay accuracy (% bias of QC samples)		
Inter-batch	91.99 – 97.57	96.23 – 107.48
Intra-batch	88.05 – 101.73	91.71 – 117.63
Bench-top stability (9 hrs.), %	102.02 – 110.98	106.25 – 108.6
Freeze-thaw stability (3 cycles), %	103.43 – 110.46	106.58 – 108.28

Source: This reviewer's compilation of the sponsor's Bioanalytical and Validation Reports for Studies PRG-NY-14-010 and PRG-NY-14-011

Validations for the LC/MS/MS bioanalytical assay of simvastatin and simvastatin acid appear acceptable with reasonable precision and accuracy.

## 3. Label Recommendations

Strikethrough text means deletion of the sponsor's proposed text. Underscored text means recommended addition. *Italicized text means internal notes and not to be communicated with the sponsor.*

## HIGHLIGHTS OF PRESCRIBING INFORMATION DOSAGE AND ADMINISTRATION

Recommended usual starting dose is 10 or 20 mg once a day in the evening on an empty stomach. (2.1)

### 2.1 Recommended Dosing

The recommended usual starting dose is 10 or 20 mg once a day (b) (4) on an empty stomach.

### 2.4 Patients with Homozygous Familial Hypercholesterolemia

The recommended dosage is 40 mg /day in the evening on an empty stomach [see Dosage and Administration, Restricted Dosing for 80 mg (2.2)].

### 2.5 Adolescents (10 to 17 years of age) with Heterozygous Familial Hypercholesterolemia

The recommended usual starting dose is 10 mg once a day in the evening on an empty stomach.

*The original Zocor clinical studies to lower cholesterol were practically conducted under empty stomach such as the 4S study (taken before the evening meal) (Lancet 1994;344:1383-9). Subsequent outcome studies were conducted with dosing and administration in the evening.*

## 12.3 Pharmacokinetics

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding  $\beta$ -hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the  $\beta$ -hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.

(b) (4)

*To be consistent with other products labels because other products labels do not contain bioequivalence study data.*

In a food effect study for simvastatin oral suspension, subjects who ate a high fat meal (b) (4) about 540 calories and 56% fat demonstrated a (b) (4) 17.5% decrease in simvastatin  $AUC_{0-\infty}$  and a (b) (4) 43.8% increase in  $\beta$ -hydroxyacid simvastatin  $AUC_{0-\infty}$ . (b) (4) -beyond what was observed in the fasted state.

*See Question 2.3.3 above.*

(b) (4)

*This is a conjecture. We do not allow statements without data in the product label.*

## 4 Appendix

### 4.1 Individual Study Synopsis

<b>Name of Sponsor:</b> Rosemont Pharmaceuticals Ltd.	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		

#### SYNOPSIS

##### Title of Study:

An open-label, balanced, randomized, reference replicate, single oral dose, two-treatment, three period, three-way crossover relative bioavailability study of Simvastatin 40mg/5 mL Oral Suspension of Rosemont Pharmaceuticals Ltd. and Zocor<sup>®</sup> (Simvastatin) 80 mg tablets of Merck &Co., Inc., following a single oral 80 mg dose administration (either one 80mg tablet or 10 mL of suspension) in healthy, adult, human male and/or female study participants under fasting conditions.

**Investigators:** Principal Investigator – Dr. Sudershan Vishwanath MD (b) (4)

**Study Centre:** (b) (4)

##### References:

1. Zocor<sup>®</sup> (Simvastatin) 80 mg tablets package insert available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/019766s087s088lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019766s087s088lbl.pdf) accessed on 17 October 2013.
2. Retention of bioavailability/bioequivalence samples, 21CFR320.38 and 21CFR 320.63 available at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=320&showFR=1&subpartNode=21:5.0.1.1.7.2> accessed 17 October 2013

(b) (4)

##### Study Period:

Study Start Date: 28 Dec 2013 (initial date of Period I check-in)

Study Completion Date: 19 Jan 2014 (final date of last PK sample collection)

Final date of last participant's safety follow up visit: 31 Jan 2014

##### Objective:

To assess the single dose relative bioavailability of Simvastatin 40mg/5mL Oral Suspension of Rosemont Pharmaceuticals Ltd. and Zocor<sup>®</sup> (Simvastatin) 80 mg tablets of Merck &Co., Inc., following a single oral 80 mg dose administration (either one 80mg tablet or 10 mL of suspension) in healthy, adult, human study participants under fasting conditions.

Date: 10 Apr 2014  
Confidential

<b>Name of Sponsor:</b> Rosemont Pharmaceuticals Ltd.	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		

**Methodology:**

All study related procedures, restrictions, duration, dates and timings, information on the study formulation and confidentiality of participant data were explained clearly to the volunteers by clinical personnel at the time of obtaining informed consent and also the process of informed consent was video recorded. Volunteers who signed the consent form and showed their willingness to participate in the study were enrolled. Volunteers who satisfied the inclusion and exclusion criteria and were found to be healthy on physical examination with laboratory investigation values within reference limits were considered eligible to be admitted into the study. Volunteers whose pre-study laboratory values were outside the reference range were considered for participation provided these values were considered clinically non-significant by the Medical Investigator. The eligible volunteers reported to the study site for Period I on 28 Dec 2013, between 09:30 hours to 10:41 hours, for Period II on 07 Jan 2014, between 11:45 hours to 19:59 hours (participant 19 checked in to the facility at 21:57 hrs and was withdrawn from the study due to protocol non-compliance) and for Period III on 17 Jan 2014, between 11:57 hours to 19:28 hours.

**Study Participants and Study Activities:**

Study participants were served dinner at 20:00 to 20:31 hours at check-in to ensure a minimum of 10.0 hours fasting prior to dose administration. On the day of dosing in each period, a single dose of either the Test or Reference product was administered with 240 mL of room temperature drinking water. Dosing was conducted as per the randomization schedule in each period under fasting conditions. Following dosing in each period, a total of 20 blood samples were collected over 19 time points from 0-32 hours post-dose. Study participants were discharged from the clinical pharmacology unit (CPU) at 36 hours post-dose. A washout period of at least 07 days was observed between the periods. Study restrictions with respect to fluid intake and physical activity were implemented throughout their stay in the CPU.

**Number of Study Participants Planned:**

The planned sample size was 42.

**Number of Study Participants Analyzed:**

Plasma samples from 38 participants (excluding participants 12, 19, 21 & 41) were analyzed and pharmacokinetic analysis was performed on this data. Reference-Scaled Average Bioequivalence results were based on the data from the 36 participants who completed all three periods (excluding participants 05, 12, 19, 21, 29 & 41). Reference variability (swr) calculations were based on data from 38 subjects (excluding participants 12, 19, 21 & 41) who received the Reference drug in at least two periods.

Participants were withdrawn / excluded from the analyses above due to adverse events or non-compliance to protocol requirements.

Study No.: 12192/13-14; Protocol No.: (b) (4)/086/13-14  
 Version No.: 01

Date: 10 Apr 2014  
 Confidential

<b>Name of Sponsor:</b> Rosemont Pharmaceuticals Ltd.	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		
<b>Main Criteria for Inclusion:</b> Healthy adult participants between 18-55 years (inclusive) of age who were willing to participate in the study by providing written informed consent.		
<b>Investigational Products, Dose, Mode of Administration and Batch/Lot Number:</b>		
<b>Test Product: T</b> Simvastatin Oral Suspension 40mg/5mL Lot Number: 019236 Mfg. By: Rosemont Pharmaceuticals Ltd. Braithwaite Street, Leeds, LS11 9XE, United Kingdom Mode of Administration: Oral	<b>Reference Product: R</b> Zocor <sup>®</sup> (Simvastatin) 80 mg tablets Lot No.: J 008788 Mfd. For: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ 08889, USA By MERCK SHARP & DOHME LTD. Cramlington, Northumberland, UK NE23 3JU. Mode of Administration: Oral	
The above two products were administered as the following study treatments:		
<b>Treatment T:</b> Single oral dose of 80 mg (10mL) of Simvastatin Oral Suspension of Rosemont Pharmaceuticals Ltd. was administered after observing an overnight fast of at least 10.00 hours.		
<b>Treatment R:</b> Single oral dose of Zocor <sup>®</sup> (Simvastatin) 80 mg tablets of Merck & Co., Inc. was administered after observing an overnight fast of at least 10.00 hours.		
<b>Duration of Treatment:</b> (Check in date and Dosing day)  Period I: 28 Dec 2013 and 29 Dec 2013 Period II: 07 Jan 2014 and 08 Jan 2014 Period III: 17 Jan 2014 and 18 Jan 2014		
<b>Bioanalytical Methods:</b> Plasma samples were analyzed for Simvastatin and its metabolite (beta-hydroxyacid) using a validated LC-MS/MS method at (b) (4).		

Date: 10 Apr 2014  
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<b>Name of Sponsor:</b> Rosemont Pharmaceuticals Ltd.	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		

**Pharmacokinetic Blood Sampling:**

In each period, a total of 20 blood samples (6 mL each) were collected over 19 time points as per the following schedule:

The first two blood samples (2x6mL) were collected within 01.00 hour prior to drug administration (0.0 hour) and the others (1x6mL) at 00.33, 00.67, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 03.50, 04.00, 05.00, 06.00, 07.00, 09.00, 11.00, 14.00, 24.00 and 32.00 hours post-dose.

**Pharmacokinetic Analysis:** Based on the plasma concentrations of Simvastatin and its metabolite (beta-hydroxyacid), the following pharmacokinetic parameters were calculated by using a “non-compartmental model” for Treatments T and R:  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $C_{max}$ ,  $T_{max}$ ,  $\lambda_Z$  and  $t_{1/2}$ . All pharmacokinetic analysis was carried out using Phoenix<sup>TM</sup> WinNonlin<sup>®</sup> Ent-Version 6.3.

**Safety Assessments:** The safety assessments included monitoring of adverse events (including adverse drug reactions) as well as monitoring of vital signs at regular pre-determined intervals and as determined by the Medical Investigator. Pre-study chest X-ray, urinalysis and serology were conducted for screening of volunteers. A 12-lead ECG was recorded at the pre-study screening and at post-study. Pre-study hematology and serum chemistry assessments were done to select participants with baseline values within reference ranges, or baseline values outside the reference ranges that were deemed clinically non-significant by the Medical Investigator. Hematology and serum chemistry were repeated post-study to determine any clinically significant abnormalities. Urine drug screening was done at the time of check-in of each study period to check participants for any recent substance abuse. A clinical assessment, which included a general and systemic examination, was conducted initially at the pre-study screening. These investigations were carried out for the safety of participants and for the scientific integrity of the study.

**Descriptive Statistics:** The descriptive statistics (such as N, mean, SD, minimum, maximum, median, %CV) were calculated for all PK parameters for both Test and Reference treatments. Additionally, geometric mean was calculated for  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$ . For  $T_{max}$ , the median was reported as a descriptive statistic.

**Assessment of Bioequivalence:**

A linear mixed effects model, which included fixed effects terms for sequence, treatment, period and a random effects term for subject (sequence), was used. 90% confidence intervals for the difference between Treatment T (Test) vs. Treatment R (Reference) least-squares means comparison were calculated. The Test-to-Reference difference and the confidence interval for the log-transformed parameter were exponentiated to obtain estimates of the ratio of the Test over Reference geometric means and the 90% CI for the ratio, respectively.

<b>Name of Sponsor:</b> Rosemont Pharmaceuticals Ltd.	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		

The period and treatment effects were tested at 5% level of significance using the mean square term for the effect as the numerator and the mean square error term from the ANOVA as the denominator. The sequence effects were tested at 10% level of significance using the type III mean square term for sequence as the numerator and type III mean square for subjects nested within sequence as the denominator.

If 90% CIs of the ratio estimates for  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  were within 80.00 to 125.00%, then the Test treatment would be concluded as bioequivalent to the Reference treatment.

For any log-transformed PK parameter where the within-subject variability of the reference product was at least 0.294, bioequivalence was to be evaluated using the Scaled Average Bioequivalence (SABE) approach. Using this approach, the 95% upper confidence bounds of the Reference-scaled criterion were computed.

Scaled Average Bioequivalence for the log-transformed pharmacokinetic parameters were evaluated by testing the following null hypothesis:

$$H_0: (\mu_T - \mu_R)^2 / \sigma_{WR}^2 > \theta$$

Versus the alternative hypothesis

$$H_1: (\mu_T - \mu_R)^2 / \sigma_{WR}^2 \leq \theta$$

where  $\mu_T$  and  $\mu_R$  were the averages of the log-transformed pharmacokinetic parameters  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  for the Test and Reference products, respectively;  $\theta$  was the Scaled Average Bioequivalence limit which was calculated by the following formula:

$$\theta = \frac{(\ln \Delta)^2}{\sigma_{WO}^2}$$

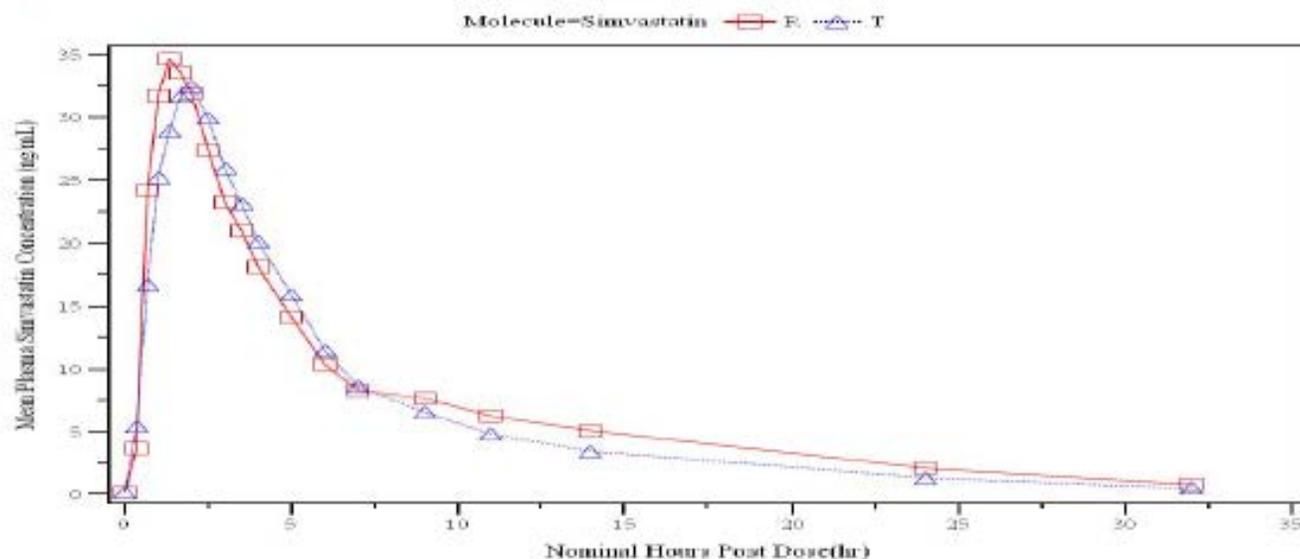
Where  $\Delta$  was 1.25, the usual average BE upper limit for the untransformed Test/Reference ratio of geometric means, and  $\sigma_{WO} = 0.25$ .

If the following two conditions were satisfied, then the Test product would be considered bioequivalent to the Reference product for the parameter:

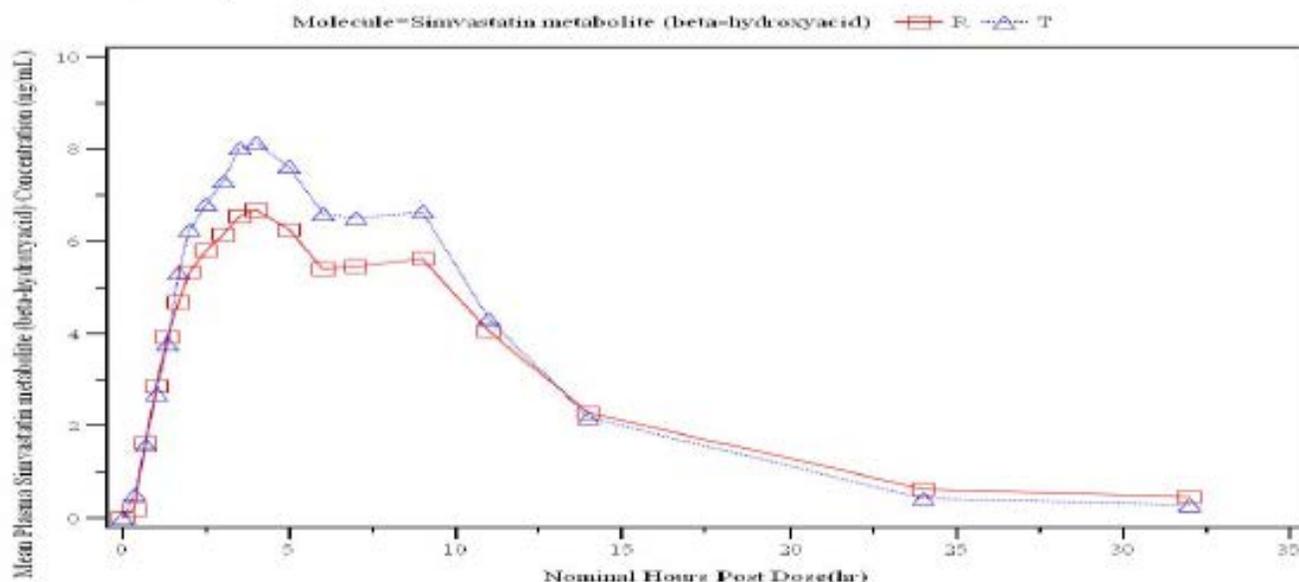
- The 95% upper confidence bound for  $(\mu_T - \mu_R)^2 / \sigma_{WR}^2 \leq \theta$ , or equivalently, the 95% upper confidence bound for  $(\mu_T - \mu_R)^2 - \theta * \sigma_{WR}^2 \leq 0$ .
- The point estimate of the Test/Reference geometric mean ratio falls within 80.00% to 125.00%.

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**Figure 1: Mean Plasma Concentrations vs Scheduled Time Plot (Linear Scale) For Simvastatin**



**Figure 2: Mean Plasma Concentrations vs Scheduled Time Plot (Linear Scale) For Simvastatin Metabolite (beta-hydroxyacid)**



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<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		
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**Pharmacokinetic Results:**

**Table 1 Mean (SD) of Pharmacokinetic Parameters of Simvastatin**

PK Parameter (Units)	Simvastatin	
	Treatment T (Test) (N=36)	Treatment R (Reference) (N=76)
C <sub>max</sub> (ng/mL)	43.754 (22.9946)	54.711 (36.1474)
AUC <sub>0-4</sub> (ng.hr/mL)	204.619 (93.2194)	227.356 (103.0450)
AUC <sub>0-∞</sub> (ng.hr/mL)	210.012 (93.7379)	235.795 (105.2573)
T <sub>max</sub> (hr)*	2.00 (0.67, 5.00)	1.33 (0.67, 5.00)
t <sub>1/2</sub> (hr)	6.404 (1.4727)	6.870 (1.7762)
Kel (1/hr)	0.114 (0.0275)	0.107 (0.0240)
AUC_Ratio (ng.hr/mL)	97.06 (2.248)	96.25 (3.053)

For T<sub>max</sub>, Median (Min, Max) are presented.

**Table 2 Mean (SD) of Pharmacokinetic Parameters of Simvastatin Metabolite (beta-hydroxyacid)**

PK Parameter (Units)	Simvastatin Metabolite (beta-hydroxyacid)	
	Treatment T (Test) (N=36)	Treatment R (Reference) (N=76)
C <sub>max</sub> (ng/mL)	9.790 (5.4606)	7.781 (3.7950)
AUC <sub>0-4</sub> (ng.hr/mL)	91.451 (48.5137)	84.384 (44.8179)
AUC <sub>0-∞</sub> (ng.hr/mL)	93.928 (49.0385)	89.405 (47.4748)
T <sub>max</sub> (hr)*	4.00 (1.00, 9.00)	4.00 (0.67, 9.00)
t <sub>1/2</sub> (hr)	5.114 (1.6734)	6.568 (2.1313)
Kel (1/hr)	0.147 (0.0421)	0.116 (0.0368)
AUC_Ratio (ng.hr/mL)	97.29 (2.820)	94.45 (5.061)

For T<sub>max</sub>, Median (Min, Max) are presented.

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<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		

**Statistical Results:**

**Table 1 Statistical Analysis Results For the Assessment of Bioequivalence Based On Log-Transformed Data of Pharmacokinetic Parameters of Simvastatin**

PK Parameter	Least Squares Geometric Means of Treatment:		Ratio (%)	Intra-subject %CV	90% CI of Ratio
	Test (T) N=36	Reference (R) N=38			
$C_{max}$ (ng/mL)	38.8401	45.2347	85.86	37.14	(75.97 , 97.05)
$AUC_{0-t}$ (ng.hr/mL)	189.5880	210.5749	90.03	27.79	(82.05 , 98.79)
$AUC_{0-\infty}$ (ng.hr/mL)	195.1368	218.9752	89.11	28.13	(81.13 , 97.89)

The 90% CI for  $AUC_{0-t}$  and  $AUC_{0-\infty}$  were within 80.00-125.00% range.

**Table 2 Statistical Analysis Results For the Assessment of Bioequivalence Based On Log-Transformed Data of Pharmacokinetic Parameters of Simvastatin (Reference Scaling Approach) (N=36)**

Parameters (Simvastatin)	Reference Variability (swr)	95% Upper Bound
$C_{max}$ (ng/mL)	0.3684899	-0.023961

For the  $C_{max}$  parameter,  $SWR > 0.294$ , hence using Scaled Average Bioequivalence (SABE) was appropriate.

Note: The above Reference-Scaled Average Bioequivalence results were estimated based on data from 36 subjects (subjects that completed all three periods) out of 38 qualified subjects, as per protocol.

Note: Reference variability (swr) calculation was based on data from 38 subjects (subjects who received the Reference drug in at least two periods).

Name of Sponsor: Rosemont Pharmaceuticals Ltd.	Individual Study Table Referring to Part of the Dossier  Volume:  Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Simvastatin Oral Suspension 40mg/5mL		
Name of Active Ingredient: Simvastatin		

**Statistical Results:**

**Table 3 Statistical Analysis Results For the Assessment of Bioequivalence Based On Log-Transformed Data of Pharmacokinetic Parameters of Simvastatin Metabolite (beta-hydroxyacid)**

PK Parameter	Least Squares Geometric Means of Treatment:		Ratio (%)	Intra-subject %CV	90% CI of Ratio
	Test (T) N=36	Reference (R) N=38			
C <sub>max</sub> (ng/mL)	8.6543	6.9238	124.99	30.33	(112.98 , 138.28)
AUC <sub>0-t</sub> (ng.hr/mL)	81.2358	75.1157	108.15	27.13	(98.76 , 118.42)
AUC <sub>0-∞</sub> (ng.hr/mL)	83.4556	79.7169	104.69	27.86	(95.38 , 114.91)

The 90% CI for AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> were within 80.00-125.00% range.

**Table 4 Statistical Analysis Results For the Assessment of Bioequivalence Based On Log-Transformed Data of Pharmacokinetic Parameters of Simvastatin Metabolite (beta-hydroxyacid) (Reference Scaling Approach) (N=36)**

Parameters (Simvastatin)	Reference Variability (swr)	95% Upper Bound
C <sub>max</sub> (ng/mL)	0.3009861	0.0369822

For the C<sub>max</sub> parameter, SWR > 0.294, hence using Scaled Average Bioequivalence (SABE) was appropriate.

Note: The above Reference-Scaled Average Bioequivalence results were estimated based on data from 36 subjects (subjects that completed all three periods) out of 38 qualified subjects, as per protocol.

Note: Reference variability (swr) calculation was based on data from 38 subjects (subjects who received the Reference drug in at least two periods).

<b>Name of Sponsor:</b> Rosemont Pharmaceuticals Ltd.	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		
<p><b>Safety Results:</b> In this study, the Test treatment was equally as tolerated as the Reference treatment, upon single-dose administration to healthy, adult, human male study participants under fasting conditions.</p> <p>A total of 03 AEs in 02 participants were reported. Of these 03 AEs, 02 AEs were reported in Period II (restlessness &amp; general body pain in participant 41), and 01 AE was observed during the post-clinical assessment (eosinophil count increased in participant 03). All AEs were considered mild in severity. Of the 03 AEs, 02 AEs were judged to be unlikely related to the study drug (eosinophil count increased in participant 03 &amp; restlessness in participant 41) and 01 AE was judged to be possibly related to the study drug (general body pain in participant 41) by the Medical Investigator. The outcomes of all AEs were resolved with no sequelae.</p>		

<b>Name of Sponsor:</b> Rosemont Pharmaceuticals Ltd.	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		
<b>Conclusion:</b>		
<b>Efficacy:</b>		
<p>Simvastatin Oral Suspension 40mg/5mL (80 mg dose; 10 mL) (Rosemont Pharmaceuticals Ltd. Braithwaite Street, Leeds, LS11 9XE, United Kingdom) (Test treatment) was determined to be bioequivalent to Zocor<sup>®</sup> (Simvastatin) 80 mg tablets (Mfd. For: Merck Sharp &amp; Dohme Corp., a subsidiary of Merck &amp; Co., Inc., Whitehouse Station, NJ 08889, USA By MERCK SHARP &amp; DOHME LTD. Cramlington, Northumberland, UK NE23 3JU) (Reference treatment) under fasting conditions.</p> <p>Based on the following criteria, bioequivalence was established: For AUC parameters, SWR &lt; 0.294, hence average bioequivalence limits were used.</p> <ul style="list-style-type: none"> <li>The 90% confidence intervals for AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> were (82.05, 98.79) and (81.13, 97.89) respectively.</li> </ul> <p>For C<sub>max</sub> parameter, SWR was 0.3684899, hence Scaled Average Bioequivalence (SABE) was used:</p> <ul style="list-style-type: none"> <li>The 95% upper bound was -0.023961, hence the 95% upper bound for C<sub>max</sub> was within the range i.e. less than or equal to zero.</li> <li>The point estimate of the Test/Reference geometric mean ratio of 85.86 was within 80.00% to 125.00%.</li> </ul> <p><b>Safety:</b></p> <p>Overall, a single 80mg (10mL) dose of Simvastatin Oral Suspension 40mg/5mL (Rosemont Pharmaceuticals Ltd. Braithwaite Street, Leeds, LS11 9XE, United Kingdom) (Test treatment) and a single dose of Zocor<sup>®</sup> (Simvastatin) 80 mg tablets, (Mfd. For: Merck Sharp &amp; Dohme Corp., a subsidiary of Merck &amp; Co., Inc., Whitehouse Station, NJ 08889, USA By MERCK SHARP &amp; DOHME LTD. Cramlington, Northumberland, UK NE23 3JU) (Reference treatment) when given under fasting conditions were equally tolerated in both treatment groups comprised of 42 healthy, adult, human male study participants.</p>		

<b>Name of Sponsor:</b> Rosemont Pharmaceuticals Ltd.	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		

**Title of Study:**

An open-label, balanced, randomized, single oral dose, one-treatment, two period, two-way crossover food effect study of Simvastatin 40mg/5mL Oral Suspension of Rosemont Pharmaceuticals Ltd., administered under fed conditions and Simvastatin 40mg/5mL Oral Suspension, administered under fasting conditions following a single oral 80 mg dose administration (10 mL) in healthy, adult, human male and/or female study participants.

**Investigators:** Principal Investigator: Dr.  
Sudershan Vishwanath MD Medical Investigator: Dr.

(b) (4)

**Study Centre:**

(b) (4)

**References:**

1. Zocor® (Simvastatin) 80 mg tablets package insert available at:  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/019766s087s088lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019766s087s088lbl.pdf)  
accessed on 18 October 2013.
2. Retention of bioavailability/bioequivalence samples, 21CFR320.38 and 21CFR 320.63 available at:  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=320&showFR=1&subpartNode=21:5.0.1.1.7.2> accessed 18 October 2013

(b) (4)

**Study Period:**

Study Start Date: 09 Jan 2014 (initial date of Period I check-in)

Study Completion Date: 21 Jan 2014 (final date of last PK sample collection)

Final date of last participant's safety follow-up visit: 27 Jan 2014

**Objective:**

To estimate the magnitude of the food effect for Simvastatin 40 mg/5 mL Oral Suspension of Rosemont Pharmaceuticals Ltd. following a single oral 80 mg dose administration (10 mL) in healthy, adult, human study participants in the fed state compared to the fasting state.

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<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		

**Methodology:**

All study related procedures, restrictions, duration, dates and timings, information on the study formulation, and confidentiality of participant data were explained clearly to the volunteers by clinical personnel at the time of obtaining informed consent and also the process of informed consent was video recorded. Volunteers who signed the consent form and showed their willingness to participate in the study were enrolled. Volunteers who satisfied the inclusion and exclusion criteria and were found to be healthy on physical examination with laboratory investigation values within reference limits were considered eligible to be admitted into the study. Volunteers whose pre-study laboratory values were outside the reference range were considered for participation provided these values were considered clinically non-significant by the Medical Investigator. The eligible volunteers reported to the study site on 09 Jan 2014 (Period I) between 10:00 hours to 11:21 hours and 19 Jan 2014 (Period II) between 11:00 hours to 19:36 hours.

**Study Participants and Study Activities:**

**Test Treatment (Fed State):**

Study participants were served dinner at 21:00 to 21:32 hours at check-in to ensure a minimum of 10.0 hours fasting prior to breakfast and dose administration. On the day of dosing in each period, participants consumed a high fat, high calorie breakfast 30 minutes before a single dose of the test product was administered with 240 mL of room temperature drinking water. Dosing was conducted as per the randomization schedule in each period under fed conditions. Following dosing in each period, a total of 20 blood samples were collected over 19 time points from 0-32 hours post-dose. Study participants were discharged from clinical pharmacology unit (CPU) at 36 hours post-dose. A washout period of at least 07 days was observed between the periods. Study restrictions with respect to fluid intake and physical activity were implemented throughout their stay in the CPU.

**Reference Treatment (Fasting State):**

Study participants were served dinner at 21:00 to 21:32 hours at check-in to ensure a minimum of 10.0 hours fasting prior to dose administration. On the day of dosing in each period, a single dose of the test product was administered with 240 mL of room temperature drinking water. Dosing was conducted as per the randomization schedule in each period. Following dosing in each period, a total of 20 blood samples were collected over 19 time points from 0-32 hours post-dose. Study participants were discharged from the clinical pharmacology unit (CPU) at 36 hours post-dose. A washout period of at least 07 days was observed between the periods. Study restrictions with respect to fluid intake and physical activity were implemented throughout their stay in the CPU.

<b>Name of Sponsor:</b> Rosemont Pharmaceuticals Ltd.	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		
<b>Number of Study Participants Planned:</b> The planned sample size was 56. Of the 70 volunteers screened, 62 were eligible for study participation: 56 were continued for dosing in Period I, and 06 reserve participants (“A”, “B”, “C”, “D”, “E” & “F”) were admitted as per (b) (4) procedure to replace pre-dose drop-out or pre-dose withdrawal participants, if necessary, in Period I only.		
<b>Number of Study Participants Analyzed:</b> Plasma samples from 52 participants (excluding participants 21, 25, 27 & 46) were analyzed and pharmacokinetic analysis was performed on this data.  Participants were withdrawn / excluded from the analyses above due to adverse events or non-compliance to protocol requirements.		
<b>Main Criteria for Inclusion:</b> Healthy adult participants between 18-55 years (inclusive) of age who were willing to participate in the study by providing written informed consent.		
<b>Investigational Products, Dose, Mode of Administration and Batch/Lot Number:</b>		
<b>Test Product</b> Simvastatin Oral Suspension 40mg/5mL Lot Number: 019236 Mfg. By: Rosemont Pharmaceuticals Ltd. Braithwaite Street, Leeds, LS11 9XE, United Kingdom Mode of Administration: Oral		
The above product was administered as the following study treatments:		
<b>Test Treatment (Fed State):</b>	Single oral dose of 80 mg (10 mL) of Simvastatin Oral Suspension of Rosemont Pharmaceuticals Ltd. was administered after a high fat, high calorie breakfast which was served after observing an overnight fast of at least 10.00 hours.	
<b>Reference Treatment (Fasting State):</b>	Single oral dose of 80 mg (10 mL) of Simvastatin Oral Suspension of Rosemont Pharmaceuticals Ltd. was administered after an observing an overnight fast of at least 10.00 hours.	

**Name of Sponsor:**

Rosemont Pharmaceuticals Ltd. **Name of Finished Product:** Simvastatin Oral Suspension  
40mg/5mL

**Name of Active Ingredient:**

Simvastatin

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Only)*

**Duration of Treatment:**

(Check in date and Dosing day)

Period I: 09 Jan 2014 and 10 Jan 2014

Period II: 19 Jan 2014 and 20 Jan 2014

**Bioanalytical Methods:** Plasma samples were analyzed for Simvastatin and its metabolite (beta-hydroxyacid) using a validated LC-MS/MS method at (b) (4)

**Pharmacokinetic Blood Sampling:**

In each period, a total of 20 blood samples (6mL each) were collected over 19 time points as per the following schedule:

The first two blood samples (2x6mL) were collected within 01.00 hour prior to drug administration (0.0 hour) and the others (1x6mL) at 00.33, 00.67, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 03.50, 04.00, 05.00, 06.00, 07.00, 09.00, 11.00, 14.00, 24.00 and 32.00 hours post-dose.

**Pharmacokinetic Analysis:** Based on the plasma concentrations of Simvastatin and its metabolite (beta-hydroxyacid), the following pharmacokinetic parameters were calculated by using “non-compartmental model” for Test Treatment (Fed State) and Reference Treatment (Fasting State):  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $C_{max}$ ,  $T_{max}$ ,  $\lambda_Z$  and  $t_{1/2}$ . All pharmacokinetic analysis was carried out using Phoenix<sup>TM</sup> WinNonlin<sup>®</sup> Ent-Version 6.3.

**Safety Assessments:** The safety assessments included monitoring of adverse events (including adverse drug reactions) as well as monitoring of vital signs at regular pre-determined intervals and as determined by the Medical Investigator. Pre-study chest X-ray, urinalysis and serology were conducted for screening of volunteers. A 12-lead ECG was recorded at the pre-study screening and at post-study. Pre-study hematology and serum chemistry assessments were done to select participants with baseline values within reference ranges, or baseline values outside the reference ranges that were deemed clinically non-significant by the Medical Investigator. Hematology and serum chemistry were repeated post-study to determine any clinically significant abnormalities. Urine drug screening was done at the time of check-in of each study period to check participants for any recent substance abuse. A clinical assessment, which included a general and systemic examination, was conducted initially at the pre-study screening. These investigations were carried out for the safety of participants and for the scientific integrity of the study.

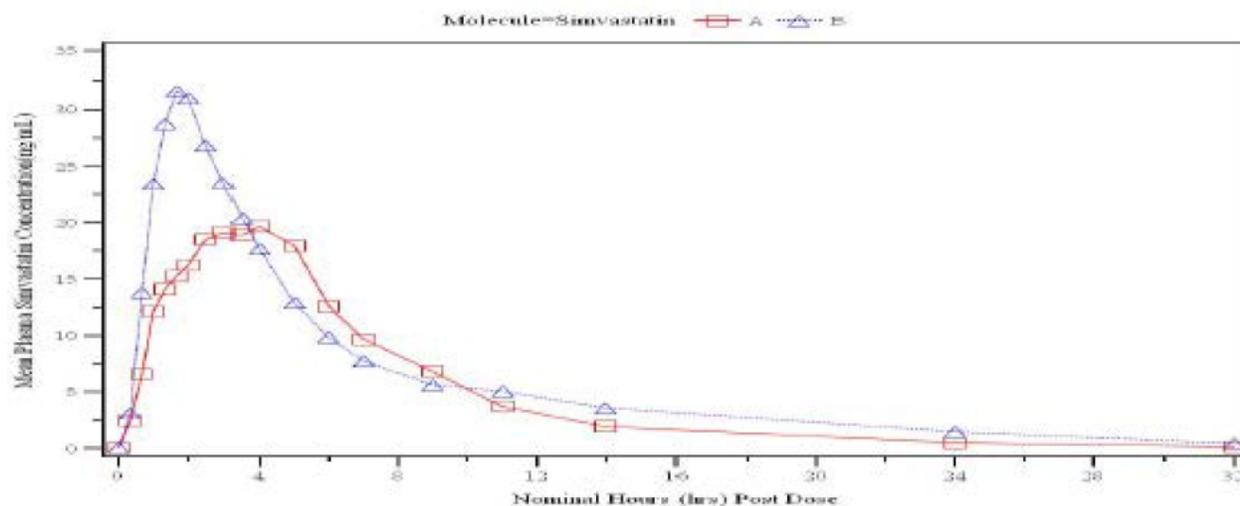
**Descriptive Statistics:** The descriptive statistics (such as N, mean, SD, minimum, maximum, median, %CV) were calculated for all PK parameters for both Test Treatment (Fed State) and Reference Treatment (Fed State). Additionally, geometric mean was calculated for  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$ . For  $T_{max}$ , the median was reported as a descriptive statistic.

<b>Name of Sponsor:</b> Rosemont Pharmaceuticals Ltd.	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		
<b>Assessment of Food Effect:</b>		
For assessment of food effect, Test Treatment (Fed State) was considered the “Test”, and Reference Treatment (Fasting State) was considered the “Reference”.		
A linear mixed effects model, which included fixed effects terms for sequence, treatment, period and a random effects term for subject (sequence) was used. 90% confidence intervals for the difference between Test Treatment (Fed State) vs Reference Treatment (Fasting State) least-squares means were calculated for log-transformed $C_{max}$ , $AUC_{0-t}$ and $AUC_{0-\infty}$ . The Test-to-Reference differences and the confidence intervals were exponentiated to obtain point estimates of the ratio of the Test over Reference geometric means and the 90% CI for the ratio, respectively.		
If 90% CIs of the ratio estimates of $C_{max}$ , $AUC_{0-t}$ and $AUC_{0-\infty}$ were within the 80.00 to 125.00%, then it would be concluded that there is no food effect.		
For the Simvastatin metabolite (beta-hydroxyacid), the following data was submitted as supportive evidence of comparable therapeutic outcome: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and $C_{max}$ .		

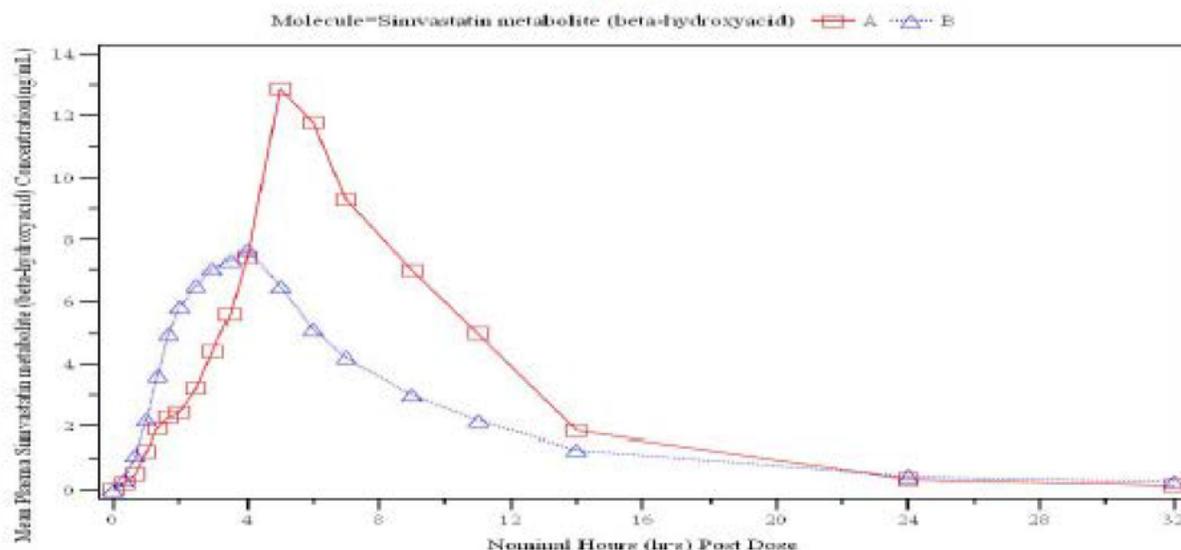
Alternate analysis was performed as deemed appropriate.

<b>Name of Sponsor:</b> Rosemont Pharmaceuticals Ltd.	<b>Individual Study Table Referring to Part of the Dossier</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		
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**Figure 1: Mean Plasma Concentrations vs Scheduled Time Plot (Linear Scale) For Simvastatin**  
(A= Fed and B= Fasting)



**Figure 2: Mean Plasma Concentrations vs Scheduled Time Plot (Linear Scale) For Simvastatin Metabolite (beta-hydroxyacid)**  
(A= Fed and B= Fasting)



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<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		

**Pharmacokinetic Results:**

**Table 1 Mean (SD) of Pharmacokinetic Parameters of Simvastatin**

PK Parameter (Units)	Simvastatin	
	Test Treatment (Fed State) (N=52)	Reference Treatment (Fasting State) (N=52)
C <sub>max</sub> (ng/mL)	26.938 (14.5492)	38.872 (26.0720)
AUC <sub>0-4</sub> (ng.hr/mL)	150.375 (82.2938)	190.284 (130.5032)
AUC <sub>0-∞</sub> (ng.hr/mL)	153.027 (82.5022)	196.627 (133.3935)
T <sub>max</sub> (hr)*	3.50 (0.67, 9.00)	1.67 (0.67, 5.00)
t <sub>1/2</sub> (hr)	4.667 (1.4636)	6.414 (2.1517)
Kel (1/hr)	0.169 (0.0689)	0.121 (0.0441)
AUC_Ratio (ng.hr/mL)	97.86 (1.157)	96.45 (2.774)

For T<sub>max</sub>, Median (Min, Max) are presented.

**Table 2 Mean (SD) of Pharmacokinetic Parameters of Simvastatin Metabolite (beta-hydroxyacid)**

PK Parameter (Units)	Simvastatin Metabolite (beta-hydroxyacid)	
	Test Treatment (Fed State) (N=52)	Reference Treatment (Fasting State) (N=52)
C <sub>max</sub> (ng/mL)	14.600 (7.7785)	8.494 (5.1502)
AUC <sub>0-4</sub> (ng.hr/mL)	95.695 (50.6424)	65.097 (36.5048)
AUC <sub>0-∞</sub> (ng.hr/mL)	96.943 (51.3847)	68.669 (39.1279)
T <sub>max</sub> (hr)*	5.50 (4.00, 9.00)	4.00 (1.33, 7.00)
t <sub>1/2</sub> (hr)	4.001 (1.3095)	6.569 (3.5356)
Kel (1/hr)	0.193 (0.0699)	0.134 (0.0622)
AUC_Ratio (ng.hr/mL)	98.73 (1.206)	95.30 (5.096)

For T<sub>max</sub>, Median (Min, Max) are presented.

<b>Name of Sponsor:</b> Rosemont Pharmaceuticals Ltd.	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)*</i>
<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		

**Statistical Results:**

**Table 1 Statistical Analysis Results For the Assessment of Food Effect Based On Log-Transformed Data of Pharmacokinetic Parameters of Simvastatin (N=52)**

PK Parameter	Least Squares Geometric Means of Treatment:		Ratio (%)	Intra-subject %CV	90% CI of Ratio
	Test Treatment (Fed State)	Reference Treatment (Fasting State)			
$C_{max}$ (ng/mL)	23.4610	31.8528	73.65	45.16	(63.92 , 84.87)
$AUC_{0-t}$ (ng.hr/mL)	130.4119	155.6543	83.78	27.18	(76.74 , 91.47)
$AUC_{0-\infty}$ (ng.hr/mL)	133.2920	161.4601	82.55	27.05	(75.65 , 90.09)

The 90% CI for  $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-\infty}$  were not within 80.00-125.00% range.

**Statistical Results:**

**Table 2 Statistical Analysis Results for the Assessment of Food Effect Based On Log-Transformed Data of Pharmacokinetic Parameters of Simvastatin Metabolite (beta-hydroxyacid) (N=52)**

PK Parameter	Least Squares Geometric Means of Treatment:		Ratio (%)	Intra-subject %CV	90% CI of Ratio
	Test Treatment (Fed State)	Reference Treatment (Fasting State)			
$C_{max}$ (ng/mL)	12.7211	7.3432	173.24	44.69	(150.55 , 199.34)
$AUC_{0-t}$ (ng.hr/mL)	84.8878	56.9066	149.17	28.02	(136.27 , 163.29)
$AUC_{0-\infty}$ (ng.hr/mL)	85.9925	59.8175	143.76	29.13	(130.88 , 157.90)

The 90% CI for  $C_{max}$ ,  $AUC_{0-t}$  and  $AUC_{0-\infty}$  were not within 80.00-125.00% range.

<b>Name of Sponsor:</b> Rosemont Pharmaceuticals Ltd.	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		

**Safety Results:**

In this study, Test Treatment (Fed State) was equally as well tolerated as Reference Treatment (Fasting State) upon single-dose administration to 56 healthy, adult, human male study participants.

A total of 03 AEs in 02 participants were reported. Of these 03 AEs, 01 AE was reported in Period I (headache in participant 21) and 02 AEs were observed during the post-clinical assessment (ALT & GGT increased in participant 16). All AEs were considered mild in severity. All 03 AEs were judged to be possibly related to the study drug by the Medical Investigator. The outcomes of all AEs were resolved with no sequelae.

<b>Name of Sponsor:</b> Rosemont Pharmaceuticals Ltd.	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Simvastatin Oral Suspension 40mg/5mL		
<b>Name of Active Ingredient:</b> Simvastatin		
<p><b>Conclusion:</b></p> <p><b>Efficacy:</b> It was determined that there is a food effect when Simvastatin Oral Suspension 40mg/5mL (80mg dose; 10mL) (Rosemont Pharmaceuticals Ltd. Braithwaite Street, Leeds, LS11 9XE, United Kingdom) is administered in a fed vs fasting state based on the comparison of the data below.</p> <p>For Simvastatin, there was a decrease in <math>C_{max}</math> (<math>\downarrow</math> 26.35%), <math>AUC_{0-t}</math> (<math>\downarrow</math> 16.22%), and <math>AUC_{0-\infty}</math> (<math>\downarrow</math> 17.45%). For <math>T_{max}</math> comparison, the fed state <math>T_{max}</math> was 3.50 hours compared to the fasting state <math>T_{max}</math> of 1.67 hours.</p> <p>For Simvastatin metabolite (beta-hydroxyacid), there was an increase in <math>C_{max}</math> (<math>\uparrow</math> 73.24%), <math>AUC_{0-t}</math> (<math>\uparrow</math> 49.17%), and <math>AUC_{0-\infty}</math> (<math>\uparrow</math> 43.76%). For <math>T_{max}</math> comparison, the fed state <math>T_{max}</math> was 5.50 hours compared to the fasting state <math>T_{max}</math> of 4.00 hours.</p> <p><b>Safety:</b> Overall, a single 80mg (10mL) dose of Simvastatin Oral Suspension 40mg/5mL (Rosemont Pharmaceuticals Ltd. Braithwaite Street, Leeds, LS11 9XE, United Kingdom) (Test Treatment (Fed State)) and a single 80mg (10mL) dose of Simvastatin Oral Suspension 40mg/5mL (Rosemont Pharmaceuticals Ltd. Braithwaite Street, Leeds, LS11 9XE, United Kingdom) (Reference Treatment (Fasting State)) were equally tolerated in both treatment groups comprised of 56 healthy, adult human male study participants.</p>		

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/s/  
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SZE W LAU  
03/17/2016

JAYABHARATHI VAIDYANATHAN  
03/17/2016

# CLINICAL PHARMACOLOGY FILING FORM

## Application Information

<b>NDA/BLA Number</b>	206-679	<b>SDN</b>	10
<b>Applicant</b>	PERRIGO PHARMACEUTICALS	<b>Submission Date</b>	June 22, 2015
<b>Generic Name</b>	Simvastatin	<b>Brand Name</b>	
<b>Drug Class</b>	Statin		
<b>Indication</b>	Treat hyperlipidemia or mixed dyslipidemia		
<b>Dosage Regimen</b>	5 mg to 40 mg once daily		
<b>Dosage Form</b>	Oral suspension	<b>Route of Administration</b>	Oral
<b>OCP Division</b>	2	<b>OND Division</b>	DMEP
<b>OCP Review Team</b>	<b>Primary Reviewer(s)</b>	<b>Secondary Reviewer/ Team Leader</b>	
<b>Division</b>	S.W. Johnny Lau	Jaya Vaidyanathan	
<b>Pharmacometrics</b>			
<b>Genomics</b>			
<b>Review Classification</b>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Expedited		
<b>Filing Date</b>	8/5/2015	<b>74-Day Letter Date</b>	9/4/2015
<b>Review Due Date</b>	3/18/2016	<b>PDUFA Goal Date</b>	4/22/2016

## Application Fileability

**Is the Clinical Pharmacology section of the application fileable?**

Yes

No

If no list reason(s)

**Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?**

Yes

No

If yes list comment(s)

See the "74-Day Letter Comments" section at the end of this review.

**Is there a need for clinical trial(s) inspection?**

Yes

No

If yes explain: Bioequivalent study (BA1386248) is the pivotal clinical study for the entire NDA submission.

## Clinical Pharmacology Package

Tabular Listing of All Human Studies	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Clinical Pharmacology Summary	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Bioanalytical and Analytical Methods	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Labeling	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

### Clinical Pharmacology Studies

Study Type	Count	Comment(s)
<b>In Vitro Studies</b>		
<input type="checkbox"/> Metabolism Characterization		
<input type="checkbox"/> Transporter Characterization		
<input type="checkbox"/> Distribution		

<input type="checkbox"/> Drug-Drug Interaction			
<b>In Vivo Studies</b>			
<b>Biopharmaceutics</b>			
<input type="checkbox"/> Absolute Bioavailability			
<input checked="" type="checkbox"/> Relative Bioavailability		Study SC02806	
<input checked="" type="checkbox"/> Bioequivalence		Study PRG-NY-14-010 (replicate reference ZOCOR)	
<input checked="" type="checkbox"/> Food Effect		Study PRG-NY-14-011 (fed/fast test simvastatin oral suspension)	
<input type="checkbox"/> Other			
<b>Human Pharmacokinetics</b>			
Healthy Subjects	<input checked="" type="checkbox"/> Single Dose		Studies PRG-NY-14-010, PRG-NY-14-011, and SC02806
	<input type="checkbox"/> Multiple Dose		
Patients	<input type="checkbox"/> Single Dose		
	<input type="checkbox"/> Multiple Dose		
<input type="checkbox"/> Mass Balance Study			
<input type="checkbox"/> Other (e.g. dose proportionality)			
<b>Intrinsic Factors</b>			
<input type="checkbox"/> Race			
<input type="checkbox"/> Sex			
<input type="checkbox"/> Geriatrics			
<input type="checkbox"/> Pediatrics			
<input type="checkbox"/> Hepatic Impairment			
<input type="checkbox"/> Renal Impairment			
<input type="checkbox"/> Genetics			
<b>Extrinsic Factors</b>			
<input type="checkbox"/> Effects on Primary Drug			
<input type="checkbox"/> Effects of Primary Drug			
<b>Pharmacodynamics</b>			
<input type="checkbox"/> Healthy Subjects			
<input type="checkbox"/> Patients			
<b>Pharmacokinetics/Pharmacodynamics</b>			
<input type="checkbox"/> Healthy Subjects			
<input type="checkbox"/> Patients			
<input type="checkbox"/> QT			
<b>Pharmacometrics</b>			
<input type="checkbox"/> Population Pharmacokinetics			
<input type="checkbox"/> Exposure-Efficacy			
<input type="checkbox"/> Exposure-Safety			
<b>Total Number of Studies</b>		<b>In Vitro</b>	<b>In Vivo</b>
<b>Total Number of Studies to be Reviewed</b>			
			3
			2

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments

1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	See Filing Memo on this review's Page 5.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Submitted pharmacokinetic data for the 40 mg/5 mL formulation. Submitted biowaiver request for the 20 mg/5 mL formulation.
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	Study PRG-NY-14-010
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
<b>Complete Application</b> 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist</b>		

<b>Data</b>		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
<b>Studies and Analysis</b>		
3. Is the appropriate pharmacokinetic information submitted?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
<b>General</b>		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

## Filing Memo

Is the 40 mg simvastatin/5 mL oral suspension tested in the bioequivalence study (PRG-NY-14-010) and food-effect study (PRG-NY-14-011) the same as the to-be-marketed 40 mg simvastatin/5 mL oral suspension?

The sponsor stated “There are no differences between the formulation of the submission batches, clinical batch, and proposed commercial formulation.” on Page 28 of 82 in the Drug Product Summary (Section 2.3.P).

Is the 80 mg ZOCOR tablets tested in the bioequivalence study (PRG-NY-14-010) the same as the US-approved and marketed 80 mg simvastatin tablets?

The sponsor stated the 80 mg ZOCOR tablets used in Study PRG-NY-14-010 is the US reference listed drug on Page 26 of 26 of the Biopharmaceutics Summary Section 2.7.1.3. Also, the Orange Book lists 80 mg ZOCOR as the reference listed drug.

What is the size of biobatches of simvastatin oral suspension used in Study PRG-NY-14-010 versus the size of commercial batches of simvastatin oral suspension?

The sponsor stated “The submission batches were manufactured at full scale-up (commercial) size. All process parameters used for the submission batches are the same as those proposed for use in commercial production and are based on historical experience with manufacture of the product for marketing in the EU.” on the Product Quality Summary, Section 2.3.P, Page 35.

Is the 20 mg simvastatin/5 mL oral suspension tested in the bioequivalence study (SC02806) the same as the to-be-marketed 20 mg simvastatin/5 mL oral suspension?

The sponsor stated “There are no differences between the formulation of the submission batches, clinical batch, and proposed commercial formulation.” on Page 28 of 82 in the Drug Product Summary (Section 2.3.P).

Is the 20 mg ZOCOR tablets tested in the bioequivalence study (SC02806) the same as the US-approved and marketed 20 mg simvastatin tablets?

No. The 20 mg ZOCOR tablets used in Study SC02806 were the 20 mg ZOCOR marketed in the UK (Page 23 of 954 on Study SC02806’s report).

### Need for Clinical Trial Inspection

Study PRG-NY-14-010 is the pivotal study that shows the relative bioavailability between the 40 mg simvastatin/5 mL oral suspension and the 80 mg ZOCOR tablets. Thus, an OSI inspection on Study PRG-NY-14-010 (An open-label, randomized, single oral dose, two-treatment, three period, three-way crossover relative bioavailability study of 80 mg Zocor<sup>®</sup> Tablets versus 10 mL of Simvastatin Oral Suspension, 40 mg/5 mL in healthy adults under fasted conditions) is appropriate.

Study PRG-NY-14-010’s Clinical Facility:

(b) (4)

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Study PRG-NY-14-010’s Analytical Facility:

(b) (4)

### Review Focus

The pivotal study (PRG-NY-14-010) used the scaled bioequivalence approach to assess bioequivalence of the test simvastatin oral suspension to the reference listed drug, 80 mg ZOCOR. This is unusual because the simvastatin fixed dose combination products with ezetimibe, niacin, or sitagliptin did not use the scaled bioequivalence approach. Moreover, the 2 guidances for simvastatin tablets (1 for orally disintegrating and the other for immediate release) do not recommend the scaled bioequivalence approach for generic products.

The proposed simvastatin oral suspension label has this language on food effect “In a food effect study for SIMVASTATIN ORAL SUSPENSION, subjects who ate a high fat meal (~540 Kcal, 56% fat) demonstrated a (b) (4) decrease in simvastatin AUC<sub>0-∞</sub> and a (b) (4) % increase in β-hydroxyacid simvastatin AUC<sub>0-∞</sub>, as well as (b) (4) beyond what was observed in the fasted state. (b) (4)

” The innovator product label has this language related to food effect “Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.”

### Comments to the Sponsor: 74-Day Letter Comments

We acknowledge the previous response in the letter dated March 21, 2014 for NDA 206-679 regarding the proposed approach to establish bioequivalence for simvastatin oral suspension. Upon further consideration, however, we have concern that the scaled bioequivalence approach used in the pivotal study (PRG-NY-14-010) to assess bioequivalence between the test simvastatin oral suspension and the reference ZOCOR tablet may not be consistent with the approach used for other approved simvastatin products to assess bioequivalence. The use of scaled bioequivalence approach to establish bioequivalence for simvastatin oral suspension will be a review issue.

In the food effect study (PRG-NY-14-011), food significantly affects the exposure of simvastatin and β-hydroxyacid simvastatin upon administration of simvastatin oral suspension when compared to that under the fasting state. However, the product label of reference product ZOCOR does not seem to show such a food effect. Thus, the food effect will be a review issue for simvastatin oral suspension.

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SZE W LAU  
08/17/2015

JAYABHARATHI VAIDYANATHAN  
08/17/2015