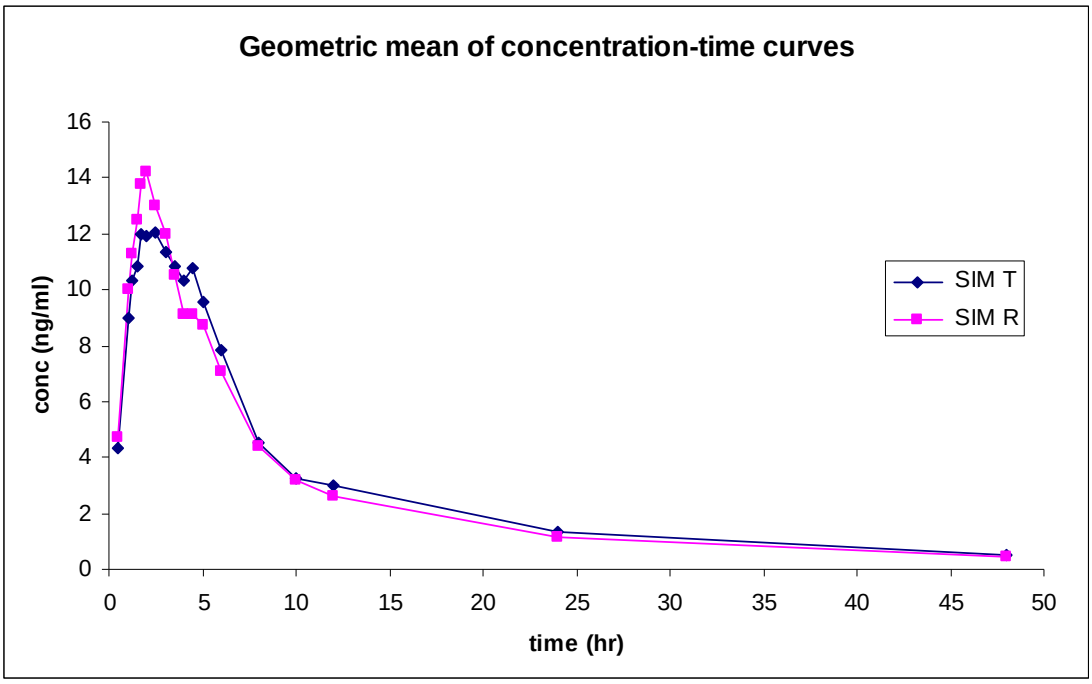
2 Study Synopsis

Title	Bioequivalence study of Simvastatin 80 mg Tablet in Healthy Thai Volunteers.
Protocol No.	**PRT-01-08**
Project No.	**SIM-001-08**
Sponsor	The Government Pharmaceutical Organization
Study site	Bio-Innova and Synchron Co. Ltd.
EC approval	The Ethical Review Committee for Research in Human Subjects, Ministry of Public Health, Bangkok, Thailand Approval Date: 23 May 2008 Approval Amendment Date: 2 December 2008
Investigators	Principal investigator: Dr. Thamnoon Vaniyapongs, MD. Clinical Investigator: Dr. Prapun Kittivoravitkul, MD
Objectives	The primary objective is to evaluate the single-dose bioequivalence of Simvastatin 80 mg tablet manufactured by the Government Pharmaceutical Organization as test formulation and Zocor® 80 mg tablet as reference formulation in healthy Thai volunteer under fasting condition. The second objective is to monitor the safety of both test and reference formulations.
Study Design	An open label, balanced randomized two-treatment, two-sequence, two-period, single-dose crossover bioequivalence study under fasting condition with 1-week washout period between the doses.
Test Product	Simvastatin 80 mg tablet, Batch/ Lot No. S510215, Mfg date 04/08/2008, Exp date 04/08/2010.
Reference Product	Zocor® 80 mg tablet, Batch/ Lot No. K2406, Mfg date 13/11/2007, Exp date 13/11/2009.

Study Subjects	34 healthy, adult volunteers were enrolled in the study to investigate the bioequivalence in 30 subjects plus 4 alternates.
Demographic Data (N=30)	Age: 24.43 ± 5.08 year Height: 166.04 ± 8.11 cm. Weight: 57.58 ± 9.26 kg. BMI: 20.76 ± 1.89 kg/m^2
Admission & Confinement	Subjects were fasted overnight at least 10 hrs prior to study drug administration. Water was allowed as desired except one hour prior to the study drug administration and two hrs after study drug administration. Standard meals were provided to each subject 4 hrs post-dose for lunch, 8 hrs post-dose for snack and 10 hrs post-dose for dinner. The subjects received identical foods in composition and amount.
Drug Administration	Each volunteer received a single dose 80 mg tablet of Simvastatin of either test or reference with 250 mL of drinking water after an overnight fasting for at least 10 hrs. The formulation was given in a crossover fashion as per the randomized schedule.
Study Period	<u>First study</u> Screening: 17, 18 and 21 November 2008 Period I: 24-26 November 2008 Period II: 1-3 December 2008 Secondary study was conducted 2 more volunteers due to 2 volunteers dropped out in study period I. Screening: 28 November 2008 Period I: 10-12 December 2008 Period II: 17-19 December 2008 Bioanalysis date: 24 November 2008-10 February 2009
Washout Period	7 days from the first study drug administration.
Safety Assessment	All adverse events, physical examination, ECGs, laboratory tests, vital signs were recorded and evaluated.
Blood Sampling Schedule	In each period, a total of 19 blood samples (7 ml each) were collected predose (0hr) and at 0.5, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8,

	10, 12, 24 and 48 hrs after dosing. The total volume of blood draw was 286 ml for each volunteer.
Blood Sampling Handling	The blood samples of Simvastatin were transferred to sample collection tubes containing EDTA as anticoagulant at each sampling time point. After blood collection, the blood samples were centrifuged at 4000 rpm for 10 minutes at 4°C and the supernatant of each sample was transferred into two aliquot labeled cryovials. All cryovials were immediately stored at -70 °C until analysis.
Clinical Samples Storage	Simvastatin and Simvastatin hydroxy acid plasma samples were stored under -70°C until analysis at Bio-Innova and Synchron Co. Ltd.
Bioanalytical Methodology	Simvastatin and Simvastatin hydroxy acid metabolite plasma concentration were assayed using a UPLC-MS/MS method. The lower limit of quantification for Simvastatin and Simvastatin acid were 0.206 ng/ml and 0.207 ng/ml, respectively.
Pharmacokinetic Parameters	Primary Pharmacokinetic Parameters; C_{max}, AUC_{0-t}, AUC_{0-inf} and Secondary Pharmacokinetic Parameters; T_{max}, K_e and $T_{1/2}$ will be determined from the plasma concentration data of analytes.
Confidence Intervals	90% CI for Geometric mean Test/Reference ratio Cmax 101.09 (87.42 - 116.90) AUC_{0-t} 104.44 (90.21 - 120.90) AUC_{0-inf} 104.08 (89.23 - 121.41)
Conclusions	The peak and total systemic exposure of Simvastatin 80 mg were similar between the 2 formulations. The 90% confidence intervals for the ratio test/reference were 87.42 to 116.90% for Cmax, 90.21to 120.90 % for AUC_{0-t} and 89.23to 121.41 % for AUC_{0-inf}. Since 90% confidence intervals for the parameters Cmax, AUC_{0-t} and AUC_{0-inf} lie within the bioequivalence range 80 to125%, it can be concluded that the Simvastatin 80 mg tablet (Test formulation: A) is bioequivalent to Zocor 80 mg tablet (reference formulation: B) under fasting condition.



Geometric means of Simvastatin plasma concentrations versus time after single dose oral administration of Simvastatin 80 mg tablet (Test formulation, the Government Pharmaceutical Organization) and Zocor® 80 mg tablet (Reference formulation) (N=30).

Final Report Issue Date	24 April 2009