

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-687

PHARMACOLOGY REVIEW(S)

MEMORANDUM

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

DATE: May 13, 2004

TO: David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
(HFD-510)

FROM: John A. Kadavil, Ph.D.
Michael F. Skelly, Ph.D.
Nilufer M. Tampal, Ph.D.
Division of Scientific Investigations (HFD-48)

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

SUBJECT: Review of EIRs Covering NDA 21-687,
Vytorin[®] (Ezetimibe/Simvastatin) Tablets,
Sponsored by MSP Singapore

At the request of HFD-510, the Division of Scientific Investigations conducted audits of the clinical and analytical portions of the following bioequivalence study:

Protocol # 039: An Open-Label, Multicenter, Randomized, 2-part, 2-period, Crossover Study to Evaluate the Definitive Bioequivalence after Concomitant Administration of Single Doses of Ezetimibe (SCH 58235, 10 mg) and Simvastatin (10 mg or 80 mg) as Individual Tablets (i.e., Ezetimibe Tablets and Simvastatin) and Final Market Image (FMI) of the Ezetimibe/Simvastatin 10/10 and 10/80 Fixed Dose Combination Tablets in Healthy Adult Subjects.

The clinical portions of the study were conducted at _____

The analytical portions of the study were conducted at Merck Research Laboratories, West Point, PA (simvastatin) and _____

Following the inspection at _____ (2/24/04 - 2/26/04), no Form FDA 483 was issued. Following the inspections at _____ (1/07/04 - 1/13/04), Merck Research Laboratories (12/15/04 - 12/19/04), and _____ (2/02/04 - 2/05/04), Forms FDA 483 were issued. The objectionable findings and our evaluations are as follows:

1. Failure to maintain adequate case histories for several subjects, specifically case report forms.

A copy of the case report form was not maintained on site for eight study subjects. _____ obtained the CRFs from the sponsor for inspection. However, there were no contradictions between the sponsor's copies of the CRFs and the supporting source documents stored on site.

_____ agreed to implement procedures to prevent this deficiency in the future.

Merck Research Laboratories, West Point, PA

1. Failure to retain the original raw data for laboratory operations and observations, and correspondence for the study.

Study-related events were recorded as word-processing files. The files were over-written during subsequent editing, thereby obscuring the times and dates of entries, as well as the identity of individuals who made the entries. The accuracy and completeness of these records cannot be confirmed.

Many records of internal and external correspondence regarding the study were not maintained at the facility. Thus, unknown amounts of correspondence were unavailable for inspection.

2. Failure to consistently integrate chromatograms for calibrators, quality controls (QCs), and study samples.

Analysts used different integration parameters to process chromatograms in individual analytical runs, for

similar concentrations of simvastatin (SV) and simvastatin acid (SVA). This resulted in errors of 25% or less, mainly at lower concentrations. Although this practice is objectionable, there is little consequence to the assessment of bioequivalence.

3. Failure to use concentrations of calibrators and QCs relevant to the expected concentrations of study samples.

The QC concentrations used in the study were 0.1, 20, and 40 ng/mL for SV and SVA. The maximum observed concentrations for Part I of the study were 15.66 ng/mL SV and 4.97 ng/mL SVA. Therefore, accuracy was only demonstrated at two concentrations, rather than the three concentrations recommended in FDA guidance.

4. Failure to validate the procedure of diluting samples with SV concentrations greater than 50 ng/mL, up to 290 ng/mL SV.

Analysts did not include dilution QCs in runs with diluted study samples to validate runs with diluted samples. Because the lactone-lactol equilibrium is influenced by protein-binding, the validity of dilution should have been demonstrated.

5. Failure to follow _____, in that some analytical runs used different amounts of SV internal standard.

The inspection revealed some runs with calibration slopes different from the theoretical 0.1 mL/ng. Examples include the analytical runs by analysts _____ between 9/27/02 and 10/30/02. Documentation for preparing the internal standard working solutions was incomplete, but _____ recalled using a partially thawed and thus unmixed SV stock solution to prepare the internal standard working solutions on at least one occasion.

Because the QCs were accurately measured in these runs, the error in preparing the internal standard working solutions has no consequence. However, the firm needs to correct deficiencies in documentation.

1. Failure to justify the re-analysis of subject samples with original results that were acceptable.

Schering-Plough (which managed _____ contract) requested reassay of about 55 subject samples for ezetimibe concentrations. Schering-Plough provided no justification for the requested reassays, and MDS did not attempt to obtain it (Form 483, item 4). Data from acceptable runs were rejected and replaced with data from the repeat runs. Approximately 36% of the reassayed samples had concentration values that differed from the initial values by more than 15%. _____ did not investigate the source of the unreliable data.

2. All study related correspondence is not maintained with study records.

For _____ Project AA01708-SDB the correspondence between the sponsor and _____ for the requested repeats was not filed with the study records. The firm needs to correct deficiencies in documentation.

Conclusion:

Following our evaluation of the inspectional findings, DSI recommends that:

1. The analytical data from Merck Research Laboratories can be accepted. However, the record keeping practices were inadequate in that raw data, such as records for preparation of solutions and reagents, extractions of calibrators, QCs, and study samples, and correspondence were not maintained. If the firm does not rectify their record keeping practices, future data could be recommended for rejection. DSI recommends that the review division mention the incomplete data and correspondence, and communicate expectations for proper record keeping in future studies in a letter to the firm.
2. Because the reason for reassaying samples for ezetimibe was not documented, the original assay values and not the reassay values at _____ should be used for bioequivalence determination.

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

John A. Kadavil, Ph.D.

Michael F. Skelly, Ph.D.

Nilufer M. Tampal, Ph.D.

Final Classifications:

NAI -

VAI -

VAI - Merck Research Laboratories, West Point, PA

VAI -

CC:

HFD-45/RF

HFD-48/Skelly(2)/Tampal(2)/Kadavil(2)/Himaya/CF

HFD-510/Orloff/NDA 21-687/IND 65-066

HFD-870/Qiu

HFR-SW1540/Martinez

HFR-SE2560/Collado

HFR-CE1515/Matusovsky

HFR-SW1575/MacInnes

Draft: NMT 3/15/04, JAK/MFS 5/13/04

Edit:

DSI: 5496; O:\BE\EIRCOVER\21687mps.vyt.doc

FACTS: 481316

Atts:

FDA-483,

FDA-483, Merck Research Laboratories

FDA-483,

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Michael Skelly

6/28/04 05:34:32 PM

PHARMACOLOGIST

(This replaces an incorrect attachment entered earlier today.) The
paper document was signed 5/20/04 by Dr. O'Shaughnessy
acting for Dr. Viswanathan.

**APPEARS THIS WAY
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M E M O R A N D U M

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

DATE: October 31, 2003

TO: Director, Investigations Branch
Dallas District Office
4040 N. Central Expy
Suite 300
Dallas, TX 75204

Director, Investigations Branch
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Suite 200
Maitland, FL 32751

Director, Investigations Branch
Philadelphia District Office
900 US Customhouse
2nd and Chestnut Streets
Room 900
Philadelphia, PA 19106

Associate Director
International Operations Drug Group
Division of Field Investigations (HFC-130)

FROM: C.T. Viswanathan, Ph.D. Nov 3, 03
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2003, **High Priority CDER User Fee NDA**, Pre-Approval
Data Validation Inspection, Bioresearch Monitoring,
Human Drugs, CP 7348.001

RE: NDA 21-687
DRUG: Vytorin[®] (Ezetimibe/simvastatin) Tablets
SPONSOR: MPS Singapore

This memo requests that you arrange for an inspection of the clinical and analytical portions of the following bioequivalence study in your respective districts. **Due to Review Division deadline, these inspections should be completed before March 31, 2004.**

Protocol Number: 039

Study Title: An Open-Label, Multicenter, Randomized, 2-part, 2-period, Crossover Study to Evaluate the Definitive Bioequivalence after Concomitant Administration of Single Doses of Ezetimibe (SCH 58235, 10 mg) and Simvastatin (10 mg or 80 mg) as Individual Tablets (i.e., Ezetimibe Tablets and Simvastatin) and Final Market Image (FMI) of the Ezetimibe/Simvastatin 10/10 and 10/80 Fixed Dose Combination Tablets in Healthy Adult Subjects.

Clinical Site

#001 (n= 96):

—
—

Clinical

Investigator:

—

Clinical Site

#003 (n= 96):

—
—

Clinical

Investigator:

—

Please check the batch numbers of both the test and the reference drug formulations used in the study with descriptions in the documents submitted to the Agency. Samples of both the test and reference drug formulations should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening.

Please have the records of all study subjects audited. The subject records in the NDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content. Dosing logs must be checked to confirm that

correct drug products were administered to the subjects. Please confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR.

Analytical Site

1: Merck Research Laboratories
West Point
PA 19486

Analytical Investigator:

Jamie Zhao, Ph.D.
Bioanalyst

Assay:

LC/MS/MS determination of simvastatin (SV)
and simvastatin acid (SVA)

Analytical Site

2:

Analytical Investigator:

Assay:

1. LC/MS/MS for determination of ezetimibe (unconjugated SCH 58235)
2. LC/MS/MS for determination of total ezetimibe (ezetimibe + ezetimibe glucuronide)

Plasma samples obtained from this study were sent to Merck Research Laboratories, West Point, PA for analysis of SV and SVA and to _____ for analysis of unconjugated and total ezetimibe (SCH 58235).

All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The chromatograms provided in the NDA submission should be compared with the original documents at the firm. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, Q.C., stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. In

Page 4 - BIMO Assignment, NDA 21-687, Vytorin
(ezetimibe/simvastatin) Tablets

Following the identification of the investigators, background material will be forwarded directly.

A member of the Bioequivalence Team from the Division of Scientific Investigations may participate in the inspections.

Headquarters Contact Person: Tamal K. Chakrabortti, Ph.D.
(301) 827-5457

CC:

HFD-45/RF
HFD-48/Chakrabortti(2)/Himaya/CF
HFD-510/Jimenez/NDA 21-687
Draft:tkc 10/31/03
Edit:MKY ~~S~~ 11/3/03
DSI:5496; O:\BE\assigns\bio21687.doc
FACTS: 481316

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10/30/03

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: October 30, 2003

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products, HFD-510

FROM: Wei Qui, Biopharmaceutical Reviewer, HFD-510

SUBJECT: Request for Biopharmaceutical Inspections
NDA 21-687
Vytorin (ezetimibe/simvastatin) Tablets

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
Protocol #039 Site #001	[REDACTED]	Merck Research laboratories West Point, PA 19486
Protocol #039 Site #003	[REDACTED]	[REDACTED]

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **January 23, 2004**. We intend to issue an action letter on this application by **February 13, 2004**.

Should you require any additional information, please contact Valerie Jimenez.

Concurrence:

David G. Orloff, M.D.

Director, Division of Metabolic and Endocrine Drug Products, HFD-510

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this page is the manifestation of the electronic signature.**

/s/

David Orloff
10/30/03 04:18:11 PM

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NDA 21-687

AP 3.30.04

Review completed: 3/29/2004
Signed off in DFS on 3/30/04

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: NDA 21-687

Review Number: 1

Sequence number/date/type of submission: September 24, 2003 (original application)

Information to sponsor: Yes () No (X)

Sponsor: MSP Singapore Company, LLC, Singapore.

Manufacturer for drug substance: The manufacturer of the combination ezetimibe/simvastatin combination tablet will be Merck & Co., Inc., NJ, USA

Reviewer name: Indra Antonipillai, Ph.D. Pharmacology Reviewer.

Division: Division of Metabolic and Endocrine Drug products, HFD #: 510

Review completion date: 3/29/2004

Drug:

Trade name: Vytorin (ezetimibe/simvastatin combination tablets), tablet strengths are 10/10, 10/20, 10/40, 10/80 mg.

Generic name (list alphabetically): Ezetimibe + simvastatin (or zetia + zocor)

Code name: combination code name is **MK-0653A**. Code name of Ezetimibe is SCH-58235, code name of simvastatin is L-654,969.

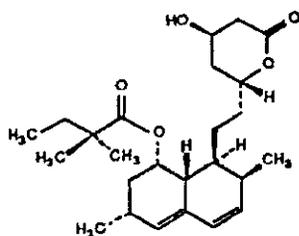
Chemical name: Ezetimibe's chemical name is 1-(4-fluorophenyl)-3-((3-(4-fluorophenyl)-3(S)-hydroxypropyl)-4(S)-4-hydroxyphenyl)-2-azetidione.

Simvastatin's chemical name is 1,2,6,7,8,8a-hexahydro-B-gamma-dihydroxy-2,6-dimethyl-8-(2,2-dimethyl-oxobutyloxy)-1-naphthaleneheptanoic acid lactone

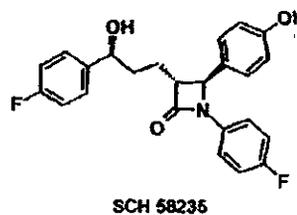
Molecular formula/molecular weight of ezetimibe: C₂₄H₂₀O₃NF₂/409.5

Molecular formula/molecular weight of simvastatin: C₂₅H₃₈O₅/418.57

Structure of simvastatin



Structure of ezetimibe



NDA 21-687

Relevant INDs/NDAs/DMFs: IND 25,742 (MK-0733, simvastatin), IND 52,791 (ezetimibe or SCH 58235), IND 65,066 (ezetimibe + simvastatin combination tablets or MK-0653A), NDA 19-766 (zocor or simvastatin tablets), NDA 21-445 (zetia or ezetimibe tablets).

Drug class: Both are lipid lowering drugs. Simvastatin is an HMG-CoA reductase inhibitor. Ezetimibe is a cholesterol absorption inhibitor (azetidinone inhibitor). Combination of two drugs has additive effects on lowering LDL-cholesterol in patients.

Indication: Treatment of hypercholesterolemia and homozygous familial hypercholesterolemia (HoFH).

Clinical formulation: The combination drug vytorin (ezetimibe /simvastatin) will be available in 10/10, 10/20, 10/40, & 10/80 mg strengths tablets. Both drugs are currently marketed drug products. These contain the active drug and inactive ingredients (see page 5).

Route of administration: Oral

Proposed use: The vytorin is indicated as an adjunctive therapy to diet for the reduction of elevated LDL-cholesterol, total cholesterol, TG, Apo B, and non-HDL-C and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed hyperlipidemia at doses in the range of 10/10-10/80 mg/day. It is also indicated in patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to other lipid lowering treatments (e.g. LDL apheresis) at the initial recommended doses of 10/40-10/80 mg/day.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise

Studies reviewed in this submission: A 14-month toxicity study in dogs with ezetimibe and simvastatin.

Studies not reviewed in this submission: None

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Executive Summary

1. Recommendations

A. Recommendation on approvability

Pharmacology recommends approval of this drug for proposed indications

B. Recommendation for Nonclinical Studies:

The preclinical studies are adequate to support the recommended doses up to 10/80 mg of zetia/zocor per day. No further pre-clinical studies are required

C. Recommendation on Labeling: No changes in labeling are recommended.

The pre-clinical labeling section for the combination is similar to approved zetia label and zocor label.

II. Summary of Nonclinical Findings:

A. Brief Review of Nonclinical studies

Both ezetimibe and simvastatin are approved drugs for oral use in USA as zetia, (NDA 21-445) and zocor (NDA 19-766). Extensive nonclinical studies have been conducted with the approved zetia and zocor. In addition sponsor has provided one non-clinical 14-month toxicity study in dogs with zetia + zocor to examine the long term effects on liver findings. The liver findings are similar to the 6-month dog combination toxicity study. The liver inflammation, bile duct hyperplasia and glycogen accumulation are partially reversible following a 3-month drug withdrawal

B. Pharmacologic activity

Both are lipid lowering drugs. Simvastatin is an HMG-CoA reductase inhibitor. Ezetimibe is a cholesterol absorption inhibitor (azetidinone inhibitor). Combination of two drugs will have additive effects on lowering LDL-cholesterol in patients.

C. Nonclinical safety issues relevant to clinical use

No new nonclinical safety issues relevant to the clinical use have been identified with the combination vytorin compared to zetia or zocor alone.

III. Administrative

A. Reviewer signature: -----

B. Supervisor signature Concurrence:-----

Non-concurrence: -----
(see memo attached)

cc: IND Arch
 HFD-510
 HFD-510/davisbruno/antonipillai/penn/parks/johnsonm
 Review code: AP
 File name: nda21687 (vytorin or ezetimibe+simvastatin)

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I. PHARMACOLOGY:

Both Zetia and zocor are lipid lowering drugs. The safety profile of simvastatin (zocor, HMG-CoA reductase inhibitor, NDA 19-766, Merck & Co.) has been well characterized, and that of ezetimibe (zetia, a cholesterol absorption inhibitor) is available from the recently approved NDA 21-445. The combination tablet contains the active drug and following inactive ingredients:

Final Market Ezetimibe/Simvastatin Combination Tablet Formulations

Composition	Unit strength (mg/tablet)			
	EZ/Simva 10 mg	EZ/Simva 20 mg	EZ/Simva 40 mg	EZ/Simva 80 mg
Ezetimibe	10.00	10.00	10.00	10.00
Simvastatin MF	10.00	20.00	40.00	80.00
Microcrystalline cellulose				
Hydroxypropyl methylcellulose				
Croscarmellose sodium				
Lactose monohydrate				
Citric acid monohydrate				
BHA				
Propyl gallate				
Magnesium stearate				
Purified Water†				
Tablet weight (mg)				

Sponsor has used basically the same formulation in the current product, as used previously for ezetimibe and simvastatin tablets, with the exception of propyl gallate (up to [redacted]) and hydroxypropyl methylcellulose (up to [redacted]). Both excipients have been used in other approved drug products in the FDA Inactive ingredient Guide (1/1996). Propyl gallate is used as intramuscular injection or topical drug at concentration of [redacted] and hydroxypropyl methyl-cellulose at doses up to of [redacted] in tablets. Some clinical studies with the above combination drugs have been conducted under IND 52,791 and IND 65,066. The other excipients like microcrystalline cellulose are used as a compression aid, lactose monohydrate as a filler (its concentration varies to compensate for the variations in drug concentration). Citric acid monohydrate is used as an acidifier to improve stability profile of simvastatin. Hydroxypropyl methyl-cellulose is used as a binder; croscarmellose sodium is used as a disintegrant to insure rapid disintegration of the tablets. Magnesium stearate is used as a lubrication agent, BHA and propyl gallate as antioxidants to improve simvastatin stability profile in a combination tablet.

Following 14-month study with ezetimibe +simvastatin in dogs has been provided in this NDA:

IV. General Toxicology:

Study title: A 14-Month Oral Toxicity Study of Ezetimibe + Simvastatin in Dogs, followed by a 3-month recovery period (Study No. 00194):

Sponsor's ID Study #: 00194

Amendment #, Vol. #, and page # : NDA 21-687, vol # C1.2, page 01.

Conducting laboratory : Schering-Plough Research Institute, Lafayette, NJ.

Date of study initiation and final report: 8/3/2001, 7/21/2003

GLP compliance: Yes

QA Report: Yes (X) No (), Is the evaluation based on a final, QA report: Yes.

Methods: This study examined the effects of ezetimibe (at 0, 0, 0.3, 1.0, 3.0 mg/kg/day) in combination with simvastatin (0, 2, 2, 2, 2 mg/kg respectively) for 14-months in dogs, followed by a 3-month drug-free recovery period in control and high dose animals.

Dosing information:

Species: Beagle dogs.

#/sex/group or time point: 4 /sex/group

Age: ≈ 5-7 months old

Weight: Males 6.6-9; females 6.1-9 kg.

satellite groups used for toxicokinetics: N/A

Dosage groups in administered units: Five groups (4 dogs/sex/group) were given oral ezetimibe by gavage (once daily) at doses of 0, 0, 0.3, 1, 3 mg/kg/day) in combination with simvastatin (0, 2, 2, 2, 2 mg/kg respectively) for 14-months. Control animals received the vehicle only. Additional 4 dogs/sex/group were added to the control and high dose group. At the end of treatment period all groups were sacrificed, except the additional control and the high dose groups (n=4/sex/dose), which were kept for additional 3 months of drug free recovery period.

Route, form, volume, and infusion rate (if i.v.): Oral (via gavage).

Drug, lot #: ezetimibe batch numbers: 99-58235-X-02, SIQ-02-EZETIMIBE-X-4003.
simvastatin batch numbers: L-644-128-000U175, L-644-128-000U176, L-644-128-000U177.

Formulation/vehicle: both formulated in aqueous methylcellulose

Table 1. Study design is presented below

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Fourteen-Month Oral (Gavage) Toxicity and Toxicokinetic Study of SCH 58235 Co-Administered with Simvastatin in Beagle Dogs with a Three-Month Postdose Period (SN 00194): Study Design						
Group	Test/Control Article	No. of Dogs/Sex ^a	Total Daily Dose (mg/kg)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Duration of Dosing (Days)
C1	Vehicle Control (Methylcellulose)	8	0	5	0	419 - 421
C2	Simvastatin Control	4	2	2.5	0.8	419 - 421
T1	Low-Dose Combination: SCH 58235 Simvastatin	4	0.3 2	2.5 2.5	0.12 0.8	419 - 421
T2	Mid-Dose Combination: SCH 58235 Simvastatin	4	1.0 2	2.5 2.5	0.4 0.8	419 - 421
T3	High-Dose Combination: SCH 58235 Simvastatin	8	3.0 2	2.5 2.5	1.2 0.8	419 - 421

a: All dogs from Groups C2, T1 and T2 and the first four dogs/sex/group from Groups C1 and T3 were sacrificed at the Week 60/61 necropsy. The remaining dogs were retained for a three-month postdose period.

Table 2. Times at which Observations are made is shown below

Fourteen-Month Oral (Gavage) Toxicity and Toxicokinetic Study of SCH 58235 Co-Administered with Simvastatin in Beagle Dogs with a Three-Month Postdose Period (SN 00194): Observations and Measurements			
Investigation	Performed	Investigation	Performed
Viability	At least once daily beginning Week -4	Hematology	Twice pretest, Weeks 11/12, 25, 39, 52, 60 and 73 ^a
Clinical Observations	Daily beginning Week -1	Coagulation	Twice pretest, Weeks 11/12, 25, 39, 52, 60 and 73 ^a
Body Weight	Weekly beginning Week -4 and day of terminal necropsy	Serum Chemistry	Twice pretest, Weeks 11/12, 25, 39, 52, 60 and 73 ^a
Food Consumption (Estimated)	Daily beginning Week -1	Urinalysis/Urine Chemistry	Twice pretest, Weeks 11/12, 25, 39, 52, 60 and 73 ^a
Ophthalmologic Examinations	Once pretest, Weeks 26, 52 and 74	Organ Weights	Yes
General Veterinary Examinations	Once pretest, Weeks 5, 25, 52 and 74	Necropsy (Macroscopic Observations)	Yes
Physical Examinations (body temperature, heart rate and blood pressure) and Electrocardiograms	Twice pretest, Weeks 6, 24, 51 and 73	Histopathology (Microscopic Observations)	Yes ^b
Plasma Analysis for SCH 58235, Simvastatin and Hydroxysimvastatin	Days 56 and 345 (1, 2, 4, 6, 12 and 24 hrs after dosing)		

a: Intervals represent scheduled collections for all surviving dogs. Additional individual samples collected.
 b: The following organs/tissues were examined microscopically: all organs/tissues collected from dogs in Groups C1 and T3 during Week 60/61; all organs/tissues collected from dogs that were sacrificed prior to scheduled necropsy; all collected gross findings; and liver from dogs in Groups T1 and T2 during Week 60/61 and dogs in Groups C1 and T3 during Week 74.

Table 3. Organs weighed: Following organs in the appended Table were weighed.

Organs Weighed	
Adrenal Glands	Pituitary Gland
Brain	Prostate Gland
Epididymides	Spleen
Heart	Testes
Kidneys	Thymus
Liver	Thyroid Gland/Parathyroid Glands
Lungs	Uterus (plus Cervix)
Ovaries	

Histopathology: At sacrifice, all organs/tissues for histopath were evaluated by the pathologist and a peer review was conducted. Groups C1, T1 through T3 were stained with hematoxylin and eosin.

Tissues Collected ^a	
Adrenal Glands	Parathyroid Gland(s)
Aorta – Thoracic	Peripheral Nerve – Sciatic
Bone (Femur, Rib ^b and Sternum)	Pituitary Gland
Bone Marrow Section – Rib ^b and Sternum	Prostate Gland
Bone Marrow for Cytology - Rib ^c	Salivary Glands – Mandibular
Brain	Skeletal Muscle – Biceps Femoris
Epididymides	Skin
Esophagus	Small Intestine – Duodenum, Jejunum, Ileum
Eyes ^d	Spinal Cord – Thoracolumbar
Gallbladder	Spleen
Heart	Stomach
Kidneys	Testes
Lacrimal Glands	Thymus
Large Intestine – Cecum and Colon	Thyroid Gland
Liver	Tongue
Lungs	Trachea
Lymph Nodes (Mandibular and Mesenteric)	Urinary Bladder
Mammary Gland	Uterus (plus Cervix)
Ovaries	Vagina
Pancreas	Animal Identification ^b

a: Collected in 10% neutral buffered formalin unless otherwise indicated
 b: Collected but not processed
 c: Bone marrow smears were prepared for all dogs but were not evaluated because it was not warranted by changes in the peripheral blood.
 d: Collected in 3% glutaraldehyde

Table 4. Liver was identified as a potential target organ of toxicity and special stains requested by the pathologist were performed as shown below:

Special Stains			
Special Stain	Tissue	Dose Group	Animal No./Sex
Acid Fast for Lipofuscin	Liver	T1	1001M
		T3	3001M, 3502F, 3503F
Lille's Iron	Liver	T1	1001M
		T3	3001M, 3502F, 3503F
Hall's Blue	Liver	T1	1001M
		T3	3001M, 3502F, 3503F
Periodic Acid-Schiff	Liver	T1	1001M
		T3	3002M, 3501F, 3504F
Oil Red O	Liver	T1	1001M
		T3	3001M, 3502F, 3503F

Toxicokinetics: Plasma concentration of the free ezetimibe and its glucuronide metabolite, as well as simvastatin and the metabolites were determined using validated LC/MS/MS.

Results:

Mortality: Three animals (one at a MD & two at a HD) were sacrificed during the study. One male (# 2002 M, sacrificed on day 40) in a MD combination group had generalized demodicosis with cutaneous skin hypersensitivity, histopath of skin revealed dermatitis and focal finding of demodex species mite contributing to skin condition. Two animals at a HD combination, one male (# 3007M, sacrificed on day 206) had arteritis in an extramural coronary artery, the other female (# 3505F, sacrificed on day 156) had gastroenteritis. These were all considered to be not drug related.

Clinical Signs: No drug related findings were observed

Body weight/Food consumption: No drug related effects were observed on body weights or on food consumption.

Ophthalmic Examination: No drug related effects were observed.

Electrocardiograms: No drug related effects were observed on body temperatures, heart rates or BPs.

Hematology: In the combination groups, prothrombin times (PTs) were increased during dosing and in week 60, these in males were 8.3, 7.8, 8.2, 8.5, 9.1 seconds at 0/0, 0/2, 0.3/2, 1/2, 3/2 mg/kg/day ezetimibe /simvastatin respectively. These values in females were 7.4, 7.7, 9.6, 8.2, 8.4 seconds respectively. During the 3-month recovery period (in week 73, these were available only in controls and HD combination) these were generally reversible (which in males were 7.8 vs 9.5 sec in controls, females were 7.9 vs 7.6 sec in controls). PT values were also slightly increased in a previous 3-month study in dogs. Reticulocyte counts remained high during dosing and recovery period in males (0.046 vs 0.023 M/ μ l in vehicle controls), this again was noted in a 3-month tox study in dogs.

Table 5. PT values in a 14-month dog toxicity study with ezetimibe + simvastatin

Test Article-Related Differences in PT Values					
Finding (Units)	Week	Group			
		Vehicle Control	Low-Dose Combination	Mid-Dose Combination	High-Dose Combination
PT (SEC)	-4/-2 ^b	—	—	—	—
		(6.3-13.2) ^f 8.06 (8.81) ^a	(7.2-8.0) 7.49	(7.1-7.9) 7.82	(6.8-13.8) 8.22 (7.22)
	60	—	0/4 ^c	1/3 (9.1)	1/7 (8.3)
		(7.3-12.7) 8.30 (9.05)	— 8.18	8.50	9.07 (7.83)
	73 (post-dose)	—	ND ^d	ND	1/3 (8.1) (7.87)
		(8.1-12.7) (9.45)	—	—	—
PT (SEC)	-4/-2 ^b	—	—	—	—
		(6.8-7.9) 7.42 (7.26)	(7.2-13.9) 9.01	(6.7-7.7) 7.24	(6.8-8.4) 7.39 (7.52)
	60	—	0/4	2/4 (7.9-8.5)	2/7 (8.8-9.2)
		(6.8-8.1) 7.43 (7.65)	9.60	8.18	8.44 (8.43)
	73 (post-dose)	—	ND	ND	0/3 — (7.93)
		(7.3-8.0) (7.60)	—	—	—

a. Only data from vehicle control and affected groups shown. All data excludes dog No. 2002M (mid-dose combination group) and dog Nos. 3007M and 3505F (high-dose combination group), which were sacrificed prior to study termination (non test article-related mortality).

b. Combined pretest data from Weeks -4 and -2.

c. (Range of individual values) Represents only those individual animals with abnormal values (except for the vehicle control group and pretest data where the range comprises all values).

d. Group mean. Calculated from all individuals within a group (followed by mean of recovery group animals only in the vehicle control and high-dose combination columns.) During Week 73, only the mean of recovery group animals is shown.

e. Incidence = Number affected/Number examined. In cases where no individuals were considered affected, group means may nevertheless be affected due to cumulative marginal differences in several individuals. Not indicated for vehicle control group.

f. ND. Not determined.

Biochemistry: In all treated dogs with the combination, minimal to marked increases in ALT were observed compared to vehicle controls during dosing period in all weeks

(week 60 values in males were 36, 45, 544, 256, 851 IU/L respectively; in females were 36, 41, 475, 965, 783 IU/L respectively). Even in LD combination group, mean ALT values were up to 100-fold higher compared to controls (males 544 vs 45 with simvastatin control). During recovery, these were reversible and ALT values were 53 vs 48 IU/L in controls. Increases in AST (week 60: males 34, 47, 70, 73, 204 IU/L respectively, females 34, 35, 88, 190, 171 IU/L respectively) and AP (week 60 males 32, 43, 86, 90, 138 IU/L respectively; females 37, 48, 140, 189, 141 respectively) were seen with all combination doses, but were reversible after discontinuation of the drug in week 73 (AP males 45 vs 24 IU/L in controls; females 51 vs 35 IU/L in controls)

Decreases in total protein, and albumin/globulin values were noted vs controls, but were reversible during recovery period. The ezetimibe + simvastatin combination at all doses decreased the serum cholesterol levels in both sexes (Week 60 males: 119, 96, 47, 33, 28 mg/dl respectively; females 162, 130, 37, 28, 37 respectively). TG values were also decreased slightly more with the combination than with simvastatin alone (males and females 11-15 vs 20-21 mg/dl with simvastatin alone). **No effects on urine analysis were observed.** The Table below shows the changes in liver enzymes.

Table 6. Changes in serum liver enzymes in male dogs in a 14-month dog toxicity study with ezetimibe + simvastatin

Test Article-Related Differences in Serum Liver Enzyme Activities: Males*					
Finding (Units)	Week	Group			
		Vehicle Control	Low-Dose Combination	Mid Dose Combination	High-Dose Combination
ALT (IU/L)	60	- (29-44) ^f 35.9 ^e	4/4 ^b (220-1199) 544.3	3/3 (103-363) 256.0	7/7 (138-1573) 851.4
	73 (post-dose)	- (29-85) 47.8	ND ^c	ND	0/3 -
AST (IU/L)	60	- (26-43) 33.6	2/4 (63-112) 69.8	2/3 (82-85) 72.7	5/7 (109-574) 204.3
	73 (post-dose)	- (32-46) 37.0	ND	ND	0/3 -
AP (IU/L)	60	- (22-52) 32.4	1/4 (130) 86.8	1/3 (144) 90.3	4/7 (103-323) 138.1
	73 (post-dose)	- (17-33) 23.8	ND	ND	0/3 -

a. Only data from vehicle control, postdose and affected groups shown.
b. Incidence = Number affected/Number examined. Not indicated for vehicle control group
c. (Range of individual values) Represents only those individual animals with abnormal values (except for the vehicle control group where the range comprises all vehicle control values).
d. Group mean. Calculated from all individuals within a group.
e. ND. Not determined

Table 7. Changes in serum liver enzymes in female dogs in a 14-month dog toxicity study with ezetimibe + simvastatin

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Test Article-Related Differences in Serum Liver Enzyme Activities: Females ^a					
Finding (Units)	Week	Dose Group (mg/kg)			
		Vehicle Control	Low-Dose Combination	Mid-Dose Combination	High-Dose Combination
ALT (IU/L)	60	— (23-66) ^c 36.3 ^d	4/4 ^b (105-1111) 474.8	4/4 (128-2808) 964.5	7/7 (59-1644) 782.9
	73 (post-dose)	— (21-43) 29.8	ND ^e	ND	0/3 — 34.0
AST (IU/L)	60	— (25-45) 33.8	1/4 (193) 88.0	2/4 (175-485) 190.3	4/7 (191-295) 171.4
	73 (post-dose)	— (25-36) 30.0	ND	ND	0/3 — 36.7
AP (IU/L)	60	— (20-49) 36.9	3/4 (87-278) 139.8	3/4 (153-271) 188.8	4/7 (147-239) 140.9
	73 (post-dose)	— (18-55) 35.3	ND	ND	0/3 — 51.3

a. Only data from vehicle control, postdose and affected groups shown.
b. Incidence = Number affected/Number examined. Not indicated for vehicle control group.
c. (Range of individual values). Represents only those individual animals with abnormal values (except for the vehicle control group where the range comprises all vehicle control values).
d. Group mean. Calculated from all individuals within a group.
e. ND: Not determined

Table 8. Organ Weights: Lower absolute and relative liver weights were observed, as shown below.

Principal Organ Weight Changes at Terminal Sacrifice: Percent Difference from Concurrent Vehicle Control Mean											
Group:	Vehicle Control		Simvastatin Control		Low-Dose Combination		Mid-Dose Combination		High-Dose Combination		
	Sex:	M	F	M	F	M	F	M	F	M	F
Organ	Mean Weight		Percent Difference from Concurrent Vehicle Control Mean (%) ^a								
Liver											
-Absolute weight	257.93 g	218.97 g	-4	+8	-17	-8	-8	-9	-23	0	
-Relative weight ^b	2.46%	2.46%	-8	+1	-14	-17	-11	-10	-18	-10	

a: Bolded and italicized values indicate a test article-related finding.
b: Relative to body weight

Table 9. Gross pathology: Small livers were observed in all combination groups of LD, MD, HD (in 2/8, 3/8, 6/10 dogs vs none in both controls).

Principal Necropsy Findings (Terminal and Unscheduled Sacrifices)											
Group:	Vehicle Control		Simvastatin Control		Low-Dose Combination		Mid-Dose Combination		High-Dose Combination		
	Sex:	M	F	M	F	M	F	M ^b	F	M ^b	F ^b
Organ/Finding	Incidence ^a										
Liver											
-Small	0/4	0/4	0/4	0/4	1/4	1/4	1/4	2/4	3/5	3/5	
-Altered surface, granular	0/4	0/4	0/4	0/4	1/4	0/4	0/4	0/4	2/5	2/5	

a: Group includes one dog that was sacrificed preterminally for incidental cause
b: Incidence = Number affected/Number examined. Bolded and italicized values indicate a test article-related finding.

Histopathology: In all combinations, liver was the target organ of toxicity in 1 to 3 of 4 dogs. These correlated with small livers, lower liver weights, and small hepatocytes in histopath findings. In livers, minimal to mild mononuclear cell infiltration was observed in dogs at all combination doses (2/8, 0/8, 4/8, 5/8, 6/10 dogs at 0/0, 0/2, 0.3/2, 1/2, 3/2 mg/kg/day ezetimibe /simvastatin respectively). Note that the liver findings were not

observed with 2 mg/kg/day of simvastatin alone and were minimal in control dogs, but of mild severity in combination groups. Pigment accumulation in liver macrophages (0/8, 5/8, 4/8, 5/10 at 0/0, 0.3/2, 1/2, 3/2 mg/kg/day ezetimibe /simvastatin respectively), glycogen accumulation (0/8, 4/8, 2/8, 5/10 respectively) and bile duct hyperplasia (0/8, 2/8, 1/8, 4/10 respectively) was similarly observed only in combination groups and not in controls or with simvastatin alone. These findings were only partially reversible, as mononuclear cell infiltration (in 3/6 vs 1/8 in controls), pigment accumulation in liver macrophages (1/6 vs 0/8 controls), bile duct hyperplasia (2/6 vs 0/8 controls), and glycogen accumulation (5/6 vs 0/8 control dogs) were still noted in dogs after 3-months of drug free recovery period. These findings are shown in the Table 10 below

Also at a HD combination in males, toxicity was observed in epididymis (in 4/5 dogs vs none in controls, these included severe aspermia in 1/5 dogs, mononuclear cell infiltration in 2/5 dogs, and vacuolation/mineralization in 2/5 dogs). Prostate was effected (minimal to mild mononuclear cell infiltration) at MD & HD (in 1/1 & 2/5 vs 0/4 control dogs). In addition toxicity was noted at a HD in lungs (minimal accumulation of alveolar macrophages/interstitial inflammation 6/10 vs 2/8 control dogs). No data are provided on prostate, epididymis, heart and lungs during the drug free recovery period in dogs, so it is unknown if these were reversible.

Sponsor stated that liver findings are class statin effects and have been reported previously with statins alone or with ezetimibe combination with statins.

Table 10. Histopath changes in a 14-month dog toxicity study of ezetimibe + simvastatin

Principal Histopathologic Findings (Terminal and Unscheduled Sacrifices)									
Group:	Vehicle Control		Low-Dose Combination		Mid-Dose Combination		High-Dose Combination		
	Sex:	M	F	M	F	M ^a	F	M ^a	F ^a
Organ/Finding/Severity	Incidence ^b								
Liver									
-Mononuclear cell infiltration, focal/multifocal									
minimal	0/4	2/4	1/4	2/4	1/4	3/4	2/5	1/5	
mild	0/4	0/4	1/4	0/4	1/4	0/4	1/5	2/5	
-Accumulation, glycogen, focal/multifocal									
minimal	0/4	0/4	2/4	1/4	0/4	1/4	1/5	0/5	
mild	0/4	0/4	0/4	0/4	1/4	0/4	1/5	3/5	
moderate	0/4	0/4	1/4	0/4	0/4	0/4	0/5	0/5	
-Pigment accumulation, macrophage									
minimal	0/4	0/4	0/4	3/4	2/4	2/4	2/5	2/5	
mild	0/4	0/4	1/4	0/4	0/4	0/4	0/5	1/5	
-Pigment accumulation, hepatocellular									
minimal	0/4	0/4	1/4	0/4	0/4	1/4	1/5	0/5	
mild	0/4	0/4	0/4	0/4	0/4	0/4	0/5	2/5	
-Hyperplasia, bile duct									
minimal	0/4	0/4	0/4	1/4	0/4	1/4	2/5	1/5	
mild	0/4	0/4	1/4	0/4	0/4	0/4	0/5	1/5	
-Small, hepatocyte, focal/multifocal									
minimal	0/4	0/4	0/4	0/4	0/4	0/4	1/5	1/5	
mild	0/4	0/4	1/4	0/4	0/4	0/4	0/5	0/5	

a: Group includes one dog sacrificed preterminally for incidental cause
b: Incidence = Number affected/Number examined. Bolded and italicized values indicate a test article-related effect.

Table 11. Reversibility of histopath findings in a 14-month dog toxicity study with ezetimibe + simvastatin

Principal Histopathologic Findings at Postdose Sacrifice				
Group:	Vehicle Control		High-Dose Combination	
	Sex:	M	F	M
Organ/Finding/Severity	Incidence ^a			
Liver^b				
-Mononuclear cell infiltration, focal/multifocal				
minimal	1/4	0/4	1/3	1/3
mild	0/4	0/4	1/3	0/3
-Accumulation, glycogen, focal/multifocal				
minimal	0/4	0/4	2/3	2/3
mild	0/4	0/4	1/3	0/3
-Pigment accumulation, macrophage				
minimal	0/4	0/4	1/3	0/3
-Hyperplasia, bile duct				
minimal	0/4	0/4	2/3	0/3

a: Incidence = Number affected/Number examined. Bolded and italicized values indicate a test article-related effect.
b: Test article-related findings occurred mainly in the caudate lobe.

Toxicokinetics. The plasma AUC values are shown in the Table below. Exposure to simvastatin and hydroxysimvastatin generally increased by 2.4 fold with the combination of ezetimibe/simvastatin vs that with simvastatin alone (on day 56 and day 345). Exposure to hydroxysimvastatin was up to 2-3 fold greater than simvastatin. Exposure to total SCH 58235 increased with the dose. No sex related differences were noted in exposures to ezetimibe or simvastatin-hydroxysimvastatin. Previously in a 3-month dog study with the combination, the total ezetimibe drug exposure (drug+glucuronide) was not altered

Table 12. Studies in dogs: Ezetimibe (unconjugated, conjugated and total) and simvastatin & hydroxysimvastatin exposures in a 14-month dog study with ezetimibe/simvastatin.

Mean (CV) AUC(0-24 hr) of Unconjugated SCH 58235, Conjugated SCH 58235, Total SCH 58235, Simvastatin, and Hydroxysimvastatin (Male and Female Dogs Combined)											
Day	Dose ^a	AUC(0-24 hr) (ng-hr/mL)									
		Unconjugated SCH 58235		Conjugated SCH 58235		Total SCH 58235		Simvastatin		Hydroxy-Simvastatin	
		Mean	CV	Mean	CV	Mean	CV	Mean	CV	Mean	CV
56	0/2	NA	NA	NA	NA	NA	NA	28.5	55	41.0	37
	0.3/2	1.92	41	37.0	59	38.9	57	46.0	81	66.0	62
	1/2	9.41	62	199	85	208	84	41.4	35	75.9	47
	3/2	41.2	77	867	122	909	118	62.1	57	99.1	70
345	0/2	NA	NA	NA	NA	NA	NA	25.1	34	48.9	38
	0.3/2	2.08	82	67.2	59	64.1	59	51.3	63	85.8	48
	1/2	6.70	30	158	60	165	57	34.3	50	89.3	54
	3/2	40.0	80	768	45	793	47	60.6	56	117	47

a: SCH 58235 dose (mg/kg)/Simvastatin dose (mg/kg)
NA: Not applicable

Toxicology summary: In a 14-month combination toxicity study in dogs with a 3-month recovery period, doses of 0/0, 0/2, 0.3/2, 1/2, 3/2 mg/kg/day of ezetimibe/simvastatin were used. The total ezetimibe drug exposure increased with the dose (AUC_{0-24h} values in M+F of drug + glucuronide were 64, 165, 793 ng/ml.hr at 0.3/2, 1/2, 3/2 mg/kg/day of ezetimibe /simvastatin respectively). However, exposure to simvastatin and hydroxysimvastatin increased by 2.4 fold with the combination (34-61 ng.h/ml), when compared to simvastatin alone (25 ng.h/ml). Exposure to hydroxysimvastatin was up to 2-3 fold greater than simvastatin. In all combination groups, serum ALT increased (minimal to marked) compared to vehicle controls from week 11 onwards till week 60 (256-851 vs 36-45 IU/L in controls). **During recovery, elevations in liver enzymes were reversible in the HD combination vs controls (53 vs 48 IU/L in controls).** In high dose combination, AST (week 60: 204 vs 34 IU/L in controls) and AP (138 vs 32 IU/L in controls) also increased but these were partially or completely reversible after discontinuation of the drug. Liver was the target organ of toxicity. In the gross pathology, livers were not only small in all combination groups (2/8, 3/8, 6/10 at LD-HD vs none in controls), but had histopathology findings including pigment accumulation in liver macrophages (0/8, 5/8, 4/8, 5/10 at 0/0, 0.3/2, 1/2, 3/2 mg/kg/day ezetimibe /simvastatin respectively), glycogen accumulation (0/8, 4/8, 2/8, 5/10 respectively) and bile duct hyperplasia (0/8, 2/8, 1/8, 4/10 respectively). These findings were only partially reversible, as mononuclear cell infiltration (in 3/6 vs 1/8 in controls), pigment accumulation in liver macrophages (1/6 vs 0/8 controls), bile duct hyperplasia (2/6 vs 0/8 controls), and glycogen accumulation (5/6 vs 0/8 control dogs) were still observed after 3-months of drug free recovery period in both sexes. Sponsor states that these histopathology changes in the liver are similar to what is noted in a 6-month tox study with this combination in dogs. Suggesting no further progression of changes is observed. These histopathology changes in HD combination are suggestive of adaptive morphological responses related to altered lipid metabolism as seen by profound changes in serum cholesterol. **The tolerated doses or NOAEL of the combination drug in 14-month toxicity (0/0, 0/2, 0.3/2, 1/2, 3/2 mg/kg/day of ezetimibe/simvastatin) study in dogs could not be established since liver histopathology was observed even in low dose combo groups in dogs, as was noted in previous 3-month (0/10, 0.3/1, 3/1, 30/1, 30/10 mg/kg/day of ezetimibe/simvastatin) and 6 month tox (0.3/2, 1/2, 3/2 mg/kg/day of ezetimibe/simvastatin) studies with this combination in dogs (in NDA 21-445).**

X. DETAILED CONCLUSIONS AND RECOMMENDATIONS

The drug simvastatin is a cholesterol-lowering drug; it is an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme that catalyzes the rate-limiting step in cholesterol synthesis. Simvastatin has been marketed extensively by Merck for many years (NDA 19-766), for oral administration under the trade name zocor. Ezetimibe is a lipid lowering drug that selectively inhibits the intestinal absorption of cholesterol (azetidinone inhibitor). Ezetimibe has been marketed since 2002 (NDA 21-445) for oral administration under the trade name zetia. In the current proposal, the combination of two drugs is proposed for marketing in patients with heterozygous and homozygous hypercholesterolemia.

FOR THE EZETIMIBE PHARMACOLOGY & TOXICITY, Please see the completed NDA 21-445 review in DFS

EZETIMIBE + SIMVASTATIN TOXICOLOGY

The non-clinical toxicity studies in rats/dogs including the 3-month combination studies with ezetimibe + simvastatin, as well as repro-toxicity and geno-toxicity studies (with the above combination) have been reviewed under NDA 21-445.

Following is a brief summary of combination studies with ezetimibe (SCH-58238) + simvastatin in rats and dogs.

In a 3-month rat combination (ezetimibe + simvastatin) toxicity study, ezetimibe (or SCH-58238 doses of 50, 250, and 250 mg/kg/day in males and 12, 50, and 50 mg/kg/day in females by diet) was used, in combination with 10, 10, and 50 mg/kg/day of simvastatin. In addition one group of rats received simvastatin alone at 50 mg/kg/day. The total ezetimibe drug (drug + glucuronide) exposure was increased in rats on day 57 vs day 1 (AUC_{0-24h} values in males at high dose combination were 48.6 vs 9.5 µg/ml.hr on day 57 vs day 1, in females these values were 14.6 vs 4.0 µg/ml.hr). The accumulation ratios were between 0.9-5.3. The combination not only increased the simvastatin and hydroxysimvastatin exposure by up to 2-6 fold than with simvastatin alone, but also increased the ezetimibe total drug exposure in males by up to 4 fold (at a high dose combinations), not so in females. This suggests drug metabolism interaction in rats, and the hence the toxicity. All dose combinations produced decreases in mean body weight vs controls (by 6-13% in males at all doses, and by 9% in females at a high dose). High dose combination increased ALT in males (70 vs 33-57 in vehicle or simvastatin controls), AP at all doses (316-382 vs 168), & GGT at all doses (3-5 vs 12 in controls). In females liver weights increased with the combination by 60-73% vs 27-28% with simvastatin alone (7.8-9.0 vs 7.2 g with simvastatin alone). Toxicity was observed in the liver (in females at high dose combo hepatocellular hypertrophy 5/10 vs none in any controls), and stomach (acanthosis at high dose in 8/20 vs 2/20 simvastatin controls, hyperkeratosis 8/20 vs 3/20 simvastatin controls, submucosal edema 9/20 vs 1/20 in simvastatin controls). Since, at high-mid, and high-high dose combinations, there were more decreases in body weights, weight gains, increased transaminases, and histopathology changes in the liver and stomach, the tolerated doses of the combination drug in 3-month toxicity study in male rats may be 50 mg/kg/day of SCH-58235 + 10 mg/kg of simvastatin, In females the NOAEL was 12 mg/kg/day of SCH-58235 + 10 mg/kg of simvastatin.

In a 3-month dog combination (with ezetimibe + simvastatin) toxicity study with 1-month recovery period, ezetimibe (SCH-58238 doses of 0.3, 3, 30 and 30 mg/kg/day) was used in combination with 1, 1, 1, and 10 mg/kg/day of simvastatin. In addition one group of dogs received simvastatin alone at 10 mg/kg/day. The combination treatment did not alter the total ezetimibe drug exposure (AUC_{0-24h} values in M+F of drug + glucuronide at high dose combo were 4010 vs 5350 ng/ml.hr). However, exposure to simvastatin and hydroxysimvastatin increased by 2.5 and 1.7 fold, when compared to simvastatin alone. Exposure to hydroxysimvastatin was up to 5-fold greater than simvastatin. In all treated dogs, serum ALT increased (minimal to marked) compared to

vehicle controls during weeks 5, 8, and 13. In high dose combination group, mean serum ALT was 50-fold higher compared to controls (1875 vs 34 in controls, in week 13). **During recovery, half of dogs in high dose combination still had increased ALT values (130-171 vs 26-54 IU/L in controls).** In high dose combination, AST (week 13: 72-230 vs 21-44 IU/L in controls) and AP (166-729 vs 47-185 IU/L in controls) also increased but these were reversible after discontinuation of the drug, whereas glucose (83-89 vs 90-124 mg/dl in controls), total protein (4.2-5.0 vs 5.2-6.2 g/dl) and albumin (1.8-2.7 vs 2.9-3.3 g/dl in controls) were decreased. In liver, minimal hepatocytic cytoplasmic eosinophilia was observed in 1-2 dogs (in both sexes) at low-mid doses, and in all 5-6/6 dogs at high dose combination (vs 0/8 in simvastatin control dogs). Biliary hyperplasia was observed in all 4-5/6 dogs (in both sexes) at high dose combination (vs 0/8 in simvastatin control dogs). Sponsor states that these histopathology changes in liver are class statin effects, and have been reported previously. **The tolerated doses of the combination drug in 3-month toxicity study in dogs could not be established since liver histopathology was observed even in low dose combo groups in dogs.**

In a 6-month dog combination study of simvastatin (2 mg/kg/day) + SCH 58235 (0.3, 1, 3 mg/kg/day), cholesterol was decreased by 60-94% vs up to 44% with simvastatin alone in dogs. At mid-high dose combination, biliary hyperplasia was noted in some dogs (as seen in a 3-month tox study in dogs), and marked increases in ALT were not accompanied by liver necrosis. Liver weights were decreased at all combination doses, and decreased liver weights were associated with bile duct hyperplasia, and low cholesterol levels. High dose combination group had decreased prostate weights (which sponsor claims have been seen previously with cerivastatin and simvastatin in dogs). Histopathology exams at MD and HD combination showed bile duct hyperplasia (2/8 & 3/8 respectively) with mononuclear cell infiltration (in 2/8 & 5/8 dogs), and pigment accumulation (3/4 females, and 1/4 M + 2/4 F dogs). This 6-month tox study confirms the liver findings seen in the 3-month study, but here biliary hyperplasia was associated with mononuclear cell infiltration, which was not seen at 3-months. The NOAEL in 6-month tox study was 0.3 mg/kg/day of SCH 58235 + 2 mg/kg/day of simvastatin in dogs (i.e the lowest dose). The sponsor claims that this biliary hyperplasia with mononuclear cell infiltration has been well documented with atorvastatin alone in the literature in dogs and is not new, and would not pose any risk in humans because we already have experience with atorvastatin in humans. Basically 6-month toxicity study confirms what was seen in the 3-month tox study in dogs with this combination.

In a currently submitted 14-month combination toxicity study in dogs, with 3-month recovery period, ezetimibe (SCH-58238) doses of 0.3, 1, 3 mg/kg/day were used, in combination with 2 mg/kg/day of simvastatin. In addition one group of dogs received simvastatin alone at 2 mg/kg/day. Exposure to simvastatin and hydroxysimvastatin increased by 2.4 fold with all combinations (34-61 ng.h/ml) vs simvastatin alone (25 ng.h/ml). All combinations increased serum ALT (minimal to marked) compared to simvastatin or vehicle controls from week 11 onwards (in week 60 the levels were 256-851 vs 36-45 IU/L in both controls). **During recovery, these were reversible in the HD combination vs controls (53 vs 48 IU/L in controls).** In high dose combination, AST (week 60: 204 vs 34 IU/L in controls) and AP (138 vs 32 IU/L in controls) also increased but these were partially or completely reversible after discontinuation of the

drug. All combination groups produced small livers (2/8, 3/8, 6/10 at LD-HD vs none in controls), decreased liver weights (by up to 27%) and histopathology findings including pigment accumulation in liver macrophages (0/8, 5/8, 4/8, 5/10 at 0/0, 0.3/2, 1/2, 3/2 mg/kg/day ezetimibe /simvastatin respectively), glycogen accumulation (0/8, 4/8, 2/8, 5/10 respectively) and bile duct hyperplasia (0/8, 2/8, 1/8, 4/10 respectively). These findings were only partially reversible, as mononuclear cell infiltration (in 3/6 vs 1/8 in controls), pigment accumulation in liver macrophages (1/6 vs 0/8 controls), bile duct hyperplasia (2/6 vs 0/8 controls), and glycogen accumulation (5/6 vs 0/8 control dogs) were still observed after 3-months of drug free recovery period in both sexes. **The tolerated doses or NOAEL of the combination drug in 14-month toxicity study in dogs could not be established since liver histopathology was observed even in low dose combo groups in dogs, as was noted in previous 3-month and 6 month tox studies in dogs.**

Safety Evaluation:

As indicated earlier, simvastatin (NDA 19-766) & ezetimibe (NDA 21-445) are both approved drugs, simvastatin has been in the market since 1988 and is approved at doses up to 80 mg/day. There is clinical experience with this drug in adults, major toxicities are known, and are associated with myopathy and liver dysfunction. Similarly ezetimibe is an approved drug (NDA 21-445) at doses of 10 mg/day, and its toxicities are well characterized.

Extensive non-clinical studies have been conducted with the combination of ezetimibe + simvastatin in an approved NDA 21-445 (zetia). One additional non-clinical 14-month toxicity study with the above combination has been provided in dogs in this NDA. The toxicity observed in the 14-month toxicity study is similar to that seen previously in 3 and 6-month combination tox studies in the approved NDA 21-445 (for zetia). The safety margin in rats and dogs with the combination (ezetimibe + simvastatin) was low. However there is clinical experience with these two drugs under NDA 21-445 and two INDs (IND 52,791 and IND 65,066).

Supportive information for new excipients used has been provided in the combination tablets. Basically the same formulation in the current product has been used previously for ezetimibe tablets and simvastatin tablets. The two new excipients used here are propyl gallate (up to _____) and hydroxypropyl methylcellulose (up to _____). However, both excipients have been used in other approved drug products in the FDA Inactive ingredient Guide (1/1996). Propyl gallate is used as intramuscular injection or topical drug at concentration of _____ and hydroxypropyl methyl-cellulose at doses up to _____ mg in tablets.

The sponsor is proposing 10 mg/day of ezetimibe and up to 80 mg/day of simvastatin. Currently the recommended dose of ezetimibe is 10 mg/day (NDA 21-445) and of simvastatin is up to 80 mg/day in the label (NDA19-766). Thus, doses that will be used here have already been approved before. The sponsor has provided the comparative bioavailability after administration of a combination tablet vs the individual tablets and state that the plasma concentration are equivalent.

Labeling Review: The preclinical sections of the label for the combination are similar to the approved zetia label and zocor label. Therefore, no changes in the label are required.

External Recommendation: From the preclinical standpoint, approval of this application is recommended.

A. Reviewer signature: Indra Antonipillai

B. Supervisor signature Concurrence:-----

Non-concurrence: -----
(see memo attached)

cc: IND Arch
 HFD-510
 HFD-510/davisbruno/antonipillai/parks/johnsonm
 Review code: AP
 File name: nda21687a (vytorin or ezetimibe +simvastatin comb tablets)

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Indra Antonipillai
3/30/04 08:22:58 AM
PHARMACOLOGIST

No comments need to be communicated to the sponsor.
This application is recommended for approval
This application is recommended for approval. The label is
similar to the approved label for zetia and
zocor

Karen Davis-Bruno
3/30/04 09:51:00 AM
PHARMACOLOGIST
concur with recommendation

**APPEARS THIS WAY
ON ORIGINAL**