CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-356/S-019

Trade Name: Sular

Generic Name: nisoldipine

Sponsor: Sciele Pharma, Inc.

Approval Date: January 2, 2008

Purpose: To change the formulation to lower the strength and replace all current tablets (i.e., 10 mg, 20 mg, 30 mg, and 40 mg) with new lower, bioequivalent strengths (i.e., 8.5 mg, 17 mg, 25.5 mg, and 34 mg)

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APPLICATION NUMBER:

20-356/S-019

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APPLICATION NUMBER:

20-356/S-019

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-356/S-019

Sciele Pharma, Inc.
Attention: Stephanie Cooke, MS
Director, Regulatory Affairs
Suite 1800, 5 Concourse Parkway
Atlanta, Georgia 30328

Dear Ms. Cooke:

Please refer to your supplemental new drug application dated June 30, 2007, received July 2, 2007 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sular (nisoldipine) 8.5, 17, 25.5, and 34 mg Extended-release Tablets.

We acknowledge receipt of your submissions dated October 10, 24, 25, and 31, November 1 (three), 2 (two), 7, and 16, 2007.

This supplemental application proposes to change the formulation to lower the strength and replace all current tablets (i.e., 10 mg, 20 mg, 30 mg and 40 mg) with new lower, bioequivalent strengths (i.e., 8.5 mg, 17 mg, 25.5 mg and 34 mg).

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below.

1. In the first paragraph of the **CLINICAL PHARMACOLOGY/ Pharmacokinetics and Metabolism** section, the dose range should be included to read as follows:

   Nisoldipine pharmacokinetics are independent of the dose across the clinical dose range of 17 to 51 mg, with plasma concentrations proportional to dose. Nisoldipine accumulation, during multiple dosing, is predictable from a single dose.

2. In the second paragraph of the **CLINICAL PHARMACOLOGY/ Pharmacokinetics and Metabolism** section, the food effect statement in the fourth sentence of the second paragraph should be modified to read as follows:

   Nisoldipine is relatively well absorbed into the systemic circulation with 87% of the radiolabeled drug recovered in urine and feces. The absolute bioavailability of nisoldipine is about 5%. Nisoldipine's low bioavailability is due, in part, to pre-systemic metabolism in the gut wall, and this metabolism decreases from the proximal to the distal parts of the intestine. A pronounced food-effect is observed when SULAR is administered with a high-fat meal resulting in an increased peak concentration (Cmax) of up to 245%. Total exposure (AUC) is decreased by 25%. As a result, SULAR should be taken on an empty stomach (1 hour before or 2 hours after a meal).

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the enclosed labeling text for the package insert submitted on June 30, 2007. These revisions are terms of the approval of this application.

A waiver to perform a bioequivalence study of the intermediate strengths of 17 and 25.5 mg has been granted.

Based on the submitted dissolution data, the recommended final dissolution method and specifications are as follows:

Q: Strengths 8.5, 25.5, 34 mg Formulation	4 Hours 8 Hours 15 Hour
Strength 17 mg Formulation	4 Hours 8 Hours 15 Hour

An expiration date of 12 months is granted for the Sular Tablets 8.5 and 17 mg strengths and an expiration date of 18 months is granted for the 25.5 and 34 mg strengths.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Denise Hinton, Regulatory Project Manager, at (301) 796-1090.

Sincerely,
{See appended electronic signature page}
Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Norman Stockbridge

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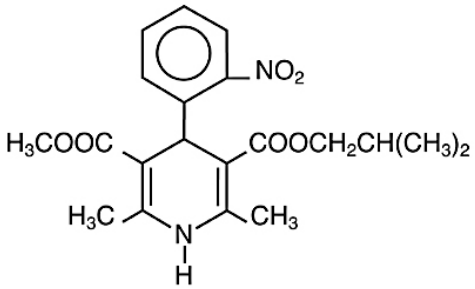
APPLICATION NUMBER:

20-356/S-019

CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF **SUPPLEMENT**

1. ORGANIZATION: ONDQA – Division of Post-Marketing Evaluation
2. NDA Number: **20-356 (Prior Approval)**
3. SUPPLEMENT NUMBERS/DATES: **SCF-019**
   Letter date: June 30, 2007
   Stamp date: July 2, 2007
4. AMENDMENTS/REPORTS/DATES: **SCF(BB)** **SCF(BC)**
   Letter date: Nov. 2, 2007 Nov. 16, 2007
   Stamp date: Nov. 5, 2007 Nov. 19, 2007
5. RECEIVED BY CHEMIST: July 18, 2007
6. APPLICANT NAME & ADDRESS: Sciele Pharma, Inc.
   Suite 1800
   5 Concourse Parkway
   Atlanta, Georgia 30328
7. NAME OF DRUG: Sular®
8. NONPROPRIETARY NAME: Nisoldipine
9. CHEMICAL NAME/STRUCTURE: 3,5-pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-methylpropyl ester
   MW: 388.4, $C_{20}H_{24}N_2O_6$



10. DOSAGE FORM(S): Tablet, Extended-Release
11. POTENCY: 10 mg, 20 mg, 30 mg, 40 mg
12. PHARMACOLOGICAL CATEGORY: Calcium channel blocker for the treatment of hypertension
13. HOW DISPENSED: X (R_X) _____ (OTC)
14. RECORDS & REPORTS CURRENT: X Yes _____ No
    REVIEW RECORDS & REPORTS CURRENT X Yes _____ No
15. RELATED IND/NDA/DMF: NA

16. SUPPLEMENT PROVIDES FOR: Replacing all strengths of the currently approved Sular® (Nisoldipine) Extended-Release Tablets 10 mg, 20 mg, 30 mg and 40 mg with newer lower, bioequivalent strengths (i.e., 8.5 mg, 17 mg, 25.5 mg and 34 mg). The new lower strengths result from a change in formulation for each strength. The change in strengths is accompanied by a change in drug product manufacturing/testing site, analytical methods and packaging components.

17. COMMENTS: In an effort to improve the currently approved Sular Extended-Release Tablets the sponsor is proposing a reformulated drug product. The sponsor's objective is to increase bioavailability while maintaining current pharmacokinetic parameters and decrease the food effect. The sponsor submitted a twenty-one volume; nine thousand plus page PA supplement to support this supplemental application. On November 1, 2007 The FDA received a major amendment to this application. On November 6, 2006 Mr. Edward Fromm, Chief, Project Management Staff, Division of Cardiovascular and Renal Products informed the sponsor that since the receipt date of this amendment was within two months of the user fee goal date the FDA was

extending the goal date for PA supplement NDA 20-356/SCF-019 by two months. The extended user fee goal date was changed from November 2, 2007 to the day after New Years, January 2, 2008.

The sponsor's pharmacokinetic and bioequivalent studies in support of this supplement have been reviewed by Dr. Lydia Velazquez, Ph.D. the Bio Pharm Reviewer in the Division of Cardiovascular and Renal Products (HFD-110) and her conclusions are contained in her January 2, 2008 memo to the file. In addition to the change in formulation for all tablet strengths, this supplement is also proposing a change in drug product manufacturing site from Bayer Healthcare AG (Leverkusen, Germany) to SkyePharma, Inc. (St. Quentin-Fallavier, France). (b) (4)

(b) (4)

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/s/

Lorenzo Rocca
1/2/2008 11:37:53 AM
CHEMIST

Jim Vidra
1/2/2008 03:45:12 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-356/S-019

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA	20-356/019	**SUBMISSION DATE**	June 30, 2007
	019BC		October 24, 2007
	019BC		October 25, 2007
	019AZ		November 1, 2007
	019BZ		November 1, 2007
	019C		November 1, 2007
	019C		November 2, 2007
	019BB		November 2, 2007
	E-mail		November 2, 2007
	019BB		November 7, 2007
	019BC		November 16, 2007

TYPE: New formulation BE Studies and Biowaiver

GENERIC NAME: Sular® (Nisoldipine Geomatrix-new formulation)
NEW DOSAGE STRENGTHS: 8.5, 17, 25.5, and 34 mg, ER oral tablets

SPONSOR: Sciele Pharma, Inc.

DIVISION OF CLINICAL PHARMACOLOGY: I
PRIMARY REVIEWER: Lydia Velazquez, Pharm.D.
TEAM LEADER: Patrick Marroum, Ph.D.

SUBMISSION

The purpose of this submission is to seek approval of a new extended release (ER) formulation for Nisoldipine (Sular®).

In an effort to improve the currently approved Sular® product, a reformulation effort was undertaken with two objectives:

1. Increase the bioavailability of orally delivered Nisoldipine while maintaining its current pharmacokinetic parameters (i.e., to create a bioequivalent formulation using less drug substance).
2. Decrease the food effect.

Sciele Pharma, Inc. intends, upon approval of this supplement, to replace all strengths of the currently approved Sular® (Nisoldipine) Extended-release Tablets (i.e., 10 mg, 20 mg, 30 mg and 40 mg) with new lower, bioequivalent strengths (i.e., 8.5 mg, 17 mg, 25.5 mg and 34 mg). The new lower strengths result from a change in formulation for each strength. Throughout this supplement, the new formulations are referred to as "Geomatrix®". A pharmacokinetics study conducted in support of this supplement demonstrated bioequivalence of the 8.5 mg Geomatrix® Tablets versus the currently approved Sular® 10 mg Tablets. Additionally, a pharmacokinetics study was conducted with the 34 mg Geomatrix® Tablets and the currently approved Sular® 40 mg Tablets, which also demonstrated bioequivalence. The resultant benefit of the bioavailability enhancement of the new Geomatrix® formulations is a 15 percent dose reduction for the patient. The secondary objective of decreasing the food effect, however, was not achieved. (b) (4)

The sponsor has submitted three bioequivalence studies (one for the highest and two studies for the lowest strength – formulations for the 8.5A and 8.5B mg strength) and is requesting a

biowaiver for the intermediate strengths (17 and 25.5 mg). An F2 similarity comparison study has been submitted in order to seek the biowaivers. In addition, a food effect study has been submitted utilizing the highest strength as referenced above. New dissolution methods and specifications specific to the new formulation were submitted and reviewed as well.

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 20-356/019 dated June 30th, October 24th and 25th, November 1st and 2nd, 7th, and 16th, 2007 and has the following comments:

REVIEWER'S COMMENTS

1. Bioequivalence between the previous extended-release formulation (10 and 40 mg) and the new Geomatrix® formulation (8.5 and 34 mg, respectively) has been established.

2. A waiver to perform a bioequivalence study of the intermediate strengths of 17 and 25.5 mg has been granted.

3. The sponsor's revised proposed dissolution methods and specifications (different for each strength) are as follows:

USP Apparatus:	II (paddle) using stationary baskets
Speed:	50 rpm
Medium:	32.5 ± 0.1g Sodium Lauryl Sulfate in 6489 mL Purified Water containing 17.0 mL Hydrochloric Acid, pH adjusted to 1.20 ± 0.05 with Hydrochloric Acid
Volume:	900 mL
Temperature:	37º C

Q:

Proposed Dissolution Specifications

(b) (4)

[redacted]

The above dissolution methods are acceptable. However, the revised proposed specifications are not acceptable since:

A. A minimum of three time points is recommended to set the specifications with an early, middle, and late stage of the dissolution profile. The last time point should be the time point where at leas (b) (4) % of the drug is dissolved or an asymptote has been reached. As a result, your proposed specification does not provide optimal control and does not provide sufficient discrimination within the specified time points.

B. Based on the submitted dissolution data submitted, the final dissolution specifications should be:

Q:		(b) (4)
Strengths 8.5, 25.5, 34 mg Formulation	**4 Hours**	
	8 Hours	
	15 Hour	
Strength 17 mg Formulation	**4 Hours**	
	8 Hours	
	15 Hour	

4. The following labeling recommendations should be addressed by the sponsor:

(b) (4)

(b) (4)

Please forward the above comments to the sponsor.

_____

_____
Lydia Velazquez, Pharm.D.
Division of Clinical Pharmacology I
Primary Reviewer

FT Initialed by Patrick Marroum, Ph.D. _____
CC list: HFD-110: NDA 20-356; HFD-860: (VelazquezL, MarroumP, MehtaM, UppoorR);
CDER Central Document Room

Appendix 1
Proposed Labeling

(b) (4)

13 PAGES OF DRAFT LABELING (B4) HAVE BEEN WITHHELD IN FULL IMMEDIATELY FOLLOWING THIS PAGE

Appendix 2 – Studies

Study 20-092-SA – SINGLE DOSE, FASTING REPLICATE CROSSOVER DESIGN COMPARATIVE BIOAVAILABILITY STUDY OF NISOLDIPINE GEOMATRIX® FORMULATION 16-E ER 34 MG TABLETS VERSUS SULAR® 40 MG ER TABELTS.

STUDY INVESTIGATOR AND SITE: James P Doherty, DO
Cedra Clinical Research, LLC
2455 NE Loop 410, Suite 150
San Antonio, TX 78217

OBJECTIVE:

The objective of this study was to compare the rate of absorption and oral bioavailability of the Test Formulation, Geomatrix 16-E, 34 mg tablets (manufactured for Sciele™ Pharma, Inc. by SkyePharma SAS) with that of the marketed Reference Product, Sular extended-release 40 mg tablets (manufactured for Sciele™ Pharma, Inc. by Bayer AG) when administered under fasting conditions of at least 10 hours.

FORMULATIONS:

Reference — Sular® ER 40 mg oral tablet (Lot #K040543A, Exp date: 09-14-2008) Manufactured for Sciele Pharma, Inc by Bayer AG.

Test — Geomatrix® 16-E, Nisoldipine ER 34 mg tablet (Lot #N736.15, Manuf date: 08-17-2006, Batch size: (b) (4)) Manufactured for Sciele Pharma, Inc by SkyePharma SAS.

STUDY DESIGN:

This was a single-dose, open-label, randomized, four-period, two-treatment, two-sequence, replicate-design crossover study in which 52 healthy male and female subjects were scheduled to receive a single dose of each of two treatments in four assigned dosing periods. Each dose administration was separated by a 7-day washout period.

The subjects were admitted to the clinical research site the evening prior to each dose administration. Subjects were evaluated to ensure that they continued to meet the inclusion/exclusion and restriction criteria. Subjects were confined to the clinical research site from approximately 12 hours before each dose administration until approximately 72 hours post dose.

Subjects were required to fast for at least 10 hours beginning the evening prior to dose administration. Each dose of study medication was administered with 240 mL of ambient temperature water. Additional water was allowed *ad lib* during the study except for 1 hour prior to dose administration through 1 hour post dose. Subjects were not permitted to lie down for 4 hours after each dose administration unless medically necessary.

Identical standard meals (consisting of caffeine-free, xanthine-free, poppy seed-free and grapefruit-free foods and beverages) were served at approximately 4 and 10 hours after drug administration and at appropriate times thereafter during the in-house confinement for each study period. Only the food served was allowed during the in-house confinement period. Please refer to the Study Menu section for specifics regarding meals or meal content.

Upon completion of the in-house confinement and each return visit for all study periods, subjects were reminded to continue to follow study restrictions regarding medications, tobacco, food and beverage intake, and exercise through the washout phase. They were also instructed regarding their return visits to the clinical research site.

ANALYTICAL METHODS:

Plasma samples were analyzed for nisoldipine by (b) (4) using validated LC-MS-MS procedures. The methods were validated for ranges of 0.0150 to 10.0 ng/mL and 1.00 to 100 pg/mL, based on the analysis of 0.250 mL and 1.00 mL of plasma, respectively.

Linearity: The assay was found to be linear over the range of 0.0150 to 10.00 ng/mL with an R^2 of $\geq$ 0.9957.

Precision and Accuracy: The CV% was 2.0 to 5.0 and %Bias was 2.3 to -2.7

Linearity: The assay was found to be linear over the range of 1.0 to 100.0 pg/mL with an R^2 of $\geq$ 0.9974

Precision and Accuracy: The CV% was 2.4 to 4.8 and %Bias was -1.7 to -7.1

SAMPLE COLLECTIONS AND PHARMACOKINETICS ANALYSIS:

Blood (plasma) pharmacokinetic characteristics were assessed after each dose of study medication.

Blood samples were drawn within 60 minutes prior to dose administration and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.5, 9.0, 10.5, 12.0, 14.0, 18.0, 24.0, 26.0, 28.0, 30.0, 36.0, 48.0, 60.0 and 72.0 hours after dose administration. Samples were collected under yellow light conditions in appropriately labeled, 6 mL Vacutainer tubes containing K_2-EDTA. For the pre-dose blood sample and each of the blood samples taken at 1.0 hour through 36.0 hours post-dose, 1 x 6 mL Vacutainer of blood was drawn. For the 48.0, 60.0 and 72.0 hours post-dose blood samples, 2 x 6 mL Vacutainers were drawn. The Clinical Listings section contains details on sample time collection deviations.

The following PK parameters for single dose ambrisentan dosing will be calculated for each formulation: C_{max}, T_{max}, $t_{½}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$, λ_z (apparent terminal elimination rate constant), and $t_{½}$.

Linear mixed effect model procedures and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max}, AUC_{last}, and AUC_{inf}. The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals of the log-transformed parameters were within 80% to 125%.

RESULTS:

A total of 52 subjects participated in the study with 44 subjects completing all four study periods. Three subjects did not dose in period 3; but returned for period 4 and completed the study.

Plasma concentration-time data and pharmacokinetic parameters were summarized by treatment. Mean concentration-time data are shown in Table S1 and Figure S1. Since subjects were scheduled to receive each treatment on two occasions, descriptive statistics by treatment are based on 93 to 95 observations. Quantifiable pre-dose concentrations were observed for some subjects. However, since the pre-dose concentrations were well below 5% of C_{max} for these subjects after a given treatment, the pre-dose concentrations were included in all pharmacokinetic analyses without adjustment.

Note: Table S1 does not add anything new to the results. So it was not provided to this review.

Results of the pharmacokinetic and statistical analyses are shown below in Tables S2 and S3. Due to the presence of secondary peaks and variability in the terminal phase of some individual profiles, lambda-z (λ_z) was estimated via linear regression of log concentration versus time data in WinNonlin. The data points that were included in the calculation were based on the regression with the largest adjusted R^2 value. This default estimation of λ_z was used throughout this study for all pharmacokinetic analyses.

Figure S1: Mean Nisoldipine Concentration-Time Profiles after Administration of Test Formulation 16-E (Geomatrix, Treatment A) and the Reference Product (Sular, Treatment B)

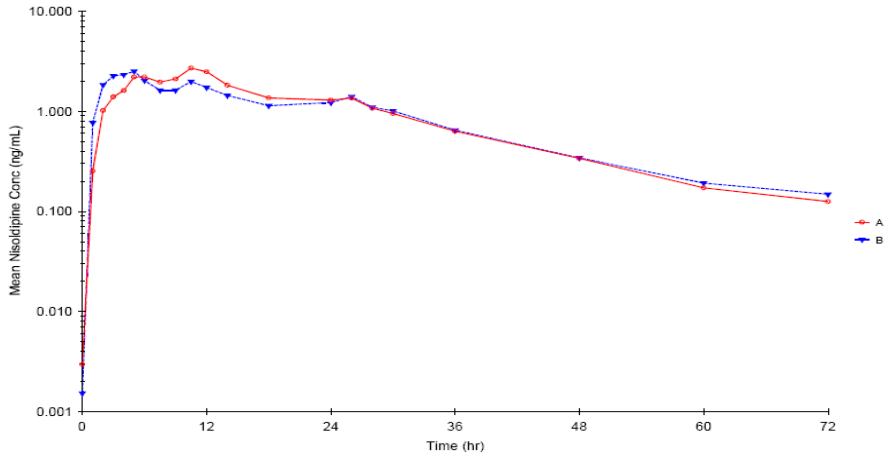


Table S2: Pharmacokinetic Parameters of Nisoldipine after Administration of Test Formulation 16-E (Geomatrix, Treatment A) and the Reference Product (Sular, Treatment B)

Parameter	Treatment A: Test Formulation 16-E (Geomatrix)				Treatment B: Reference Product (Sular)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	93	9.22	5.13	55.61	95	8.49	7.79	91.84
C_{max} (ng/mL)	93	3.79	3.56	93.97	95	3.58	3.05	85.08
AUC_{last} (hr*ng/mL)	93	62.35	69.30	111.15	95	60.10	31.52	52.45
AUC_{inf} (hr*ng/mL)	93	65.24	74.67	114.46	95	65.45	36.41	55.63
AUC_{Extrap} (%)	93	3.84	3.41	88.68	95	6.43	8.77	136.33
λ_z (hr^{-1})	93	0.0554	0.0163	29.38	95	0.0527	0.0205	38.91
$T_{1/2}$ (hr)	93	13.68	4.25	31.05	95	17.08	13.74	80.49
T_{last} (hr)	93	72.00	0.00	0.00	95	72.00	0.01	0.01
C_{last} (ng/mL)	93	0.126	0.239	190.21	95	0.148	0.166	111.91

Note: Full precision data used in pharmacokinetic analysis

Table S3: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Nisoldipine Comparing Test Formulation 16-E (Geomatrix, Treatment A) to the Reference Product (Sular, Treatment B)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power
	Test	Ref	(Test/Ref)	Lower	Upper	
$\ln(C_{max})$	3.0723	2.9941	102.61	93.61	112.47	0.9899
$\ln(AUC_{last})$	50.7356	54.6492	92.84	87.77	98.20	1.0000
$\ln(AUC_{inf})$	52.7416	58.7395	89.79	84.37	95.56	1.0000

[a] Geometric Mean for the Test Formulation (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval

SAFETY:

There were no unusual or unexpected adverse events related to the study medication. Study exit clinical laboratory, ECG, and physical examination evaluations were completed with no clinically significant findings.

The number of treatment emergent adverse events was similar between treatment groups with headache being reported as the main adverse event in all treatment arms for both reference and test formulations. None of the adverse events were severe in nature according to the sponsor; but one subject did visit the emergency room due to headache and chest pain from the reference formulation.

CONCLUSIONS:

- The 90% confidence interval for comparing the maximum exposure, based on $\ln(C_{max})$, is within the accepted 80% to 125% limits.
- The 90% confidence intervals for comparing total systemic exposure, based on $\ln(AUC_{last})$ and $\ln(AUC_{inf})$, are within the accepted 80% to 125% limits.
- Therefore, the test formulation of Geomatrix® 16-E, 34 mg tablets manufactured for Sciele™ Pharma, Inc. by SkyePharma SAS, Lyon, France, is bioequivalent to the reference product Sular® 40 mg tablets, manufactured for Sciele™ Pharma, Inc. by Bayer AG, Leverkusen, Germany, under fasting conditions.

REVIEWER'S COMMENT:

1. The reviewer concurs.

Study 20-149-SA – SINGLE DOSE, FASTING REPLICATE CROSSOVER DESIGN COMPARATIVE BIOAVAILABILITY STUDY OF NISOLDIPINE GEOMATRIX® FORMULATION 2B ER 8.5 MG TABLETS VERSUS SULAR® 10 MG ER TABLETS.

STUDY INVESTIGATOR AND SITE: James P Doherty, DO
Cedra Clinical Research, LLC
2455 NE Loop 410, Suite 150
San Antonio, TX 78217

OBJECTIVE:

To compare the rate of absorption and oral bioavailability of a test formulation Geomatrix® 2B, 8.5 mg tablets versus that of the reference product, Sular® 10 mg tablets.

FORMULATIONS:

Reference — Sular® ER 10 mg oral tablet (Lot #C060111A, Exp date: 12-01-2009) Manufactured for Sciele Pharma, Inc by Bayer AG, Leverkusen, Germany.

Test — Geomatrix® 2B, Nisoldipine ER 8.5 mg tablet (Lot #P149.09, Manuf date: 02-14-2006, Batch size: (b) (4) Manufactured for Sciele Pharma, Inc by SkyePharma SAS, Lyon France.

STUDY DESIGN:

This was a pivotal, single-dose, open-label, randomized, four-period, two-treatment, two-sequence replicate-design crossover study in which fifty-two (52) healthy adult subjects were scheduled to receive four separate single-dose administrations of nisoldipine extended-release tablets in four study periods following an overnight fast of at least 10 hours.

Attempts were made to enroll an equal number of male and female subjects.

Subjects were assigned numbers in an ascending order, based on successful completion of the screening process. Fifty-two subjects were scheduled to receive each of the treatments twice in a 2-sequence randomized fashion during the four treatment periods. Each dose administration was separated by a 7 day washout period.

The subjects were admitted to the clinical research site the evening prior to each dose administration. Subjects were evaluated to ensure that they continued to meet the inclusion/exclusion and restriction criteria. Subjects were confined to the clinical research site from approximately 12 hours before each dose administration until approximately 72 hours post dose.

Subjects were required to fast for at least 10 hours beginning the evening prior to dose. Each dose of study medication was administered with 240 mL of room temperature tap water. Additional water was allowed *ad lib* during the study except for 1 hour prior to dose administration through 1 hour post dose. Subjects were not permitted to lie down for 4 hours after each dose administration unless medically necessary.

Identical standard meals (consisting of caffeine-free, xanthine-free, and grapefruit-free foods and beverages) were provided at 4 and 10 hours after drug administration and at appropriate times thereafter. The menu for all meals and snacks consumed during research center confinement were the same for all study periods. Please refer to the Study Menu section for specifics regarding meals or meal content.
Alcohol and caffeine-containing beverages and foods (e.g., coffee, tea, cola, cocoa, chocolate) and quinine-containing products (e.g., Schweppes) were not permitted at the following times:

- From 48 hours prior to the pre-study screening until completion of screening procedures.

- At least 48 hours prior to first dose of test article until end-of-study discharge.

Poppy seed-containing food (e.g. poppy seed cake) was not allowed during the 72 hours before the pre-study examination and from 72 hours before first dose of test article until end-of-study discharge, because this could lead to a false positive result on the UDS. Foods or beverages containing grapefruit were not allowed during the entire study (14 days prior to first dose of test article until end-of-study discharge).

ANALYTICAL METHODS:

Plasma samples were analyzed for nisoldipine by (b) (4) using validated LC-MS-MS procedures. The methods were validated for ranges of 0.0150 to 10.0 ng/mL and 1.00 to 100 pg/mL, based on the analysis of 0.250 mL and 1.00 mL of plasma, respectively.

Linearity: The assay was found to be linear over the range of 0.0150 to 10.00 ng/mL with an R^2 of $\geq$ 0.9930.

Precision and Accuracy: The CV% was 2.1 to 3.8 and %Bias was 3.5 to -4.2

Linearity: The assay was found to be linear over the range of 1.0 to 100.0 pg/mL with an R^2 of $\geq$ 0.9923

Precision and Accuracy: The CV% was 1.5 to 8.6 and %Bias was 4.5 to -3.0

SAMPLE COLLECTIONS AND PHARMACOKINETICS ANALYSIS:

Blood plasma pharmacokinetic characteristics were assessed after each dose of study medication.

Blood samples were drawn 60 minutes prior to dose administration (0-hour) and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.5, 9.0, 10.5, 12.0, 14.0, 18.0, 24.0, 26.0, 28.0, 30.0, 36.0, 48.0, 60.0 and 72.0 hours after dose administration. Samples were collected in vacutainer tubes containing K_2-EDTA and kept cool until centrifugation. The Clinical Listings section contains details on sample time collection deviations.

The following PK parameters for single dose ambrisentan dosing will be calculated for each formulation: C_{max}, T_{max}, $t_{½}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, λ_z (apparent terminal elimination rate constant), and $t_{½}$.

Linear mixed effect model procedures and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max}, AUC_{last}, and AUC_{inf}. The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals of the log-transformed parameters were within 80% to 125%.

RESULTS:

A total of 52 subjects participated in the study with 45 subjects completing all study periods. Three subjects were withdrawn from the study. One was due to non-compliance with the protocol and a positive urine drug screening at period 4 check-in. Two subjects withdrew consent.

Data from 49 subjects who successfully completed at least the first two or at least the last two periods of the study (one test, one reference) without protocol violation were included in the pharmacokinetic and statistical analyses. Subject 501 experienced emesis in one study period. Although concentration-time data were acquired for Subject 501 in all study periods and retained in the data listing, Subject 501 was excluded from the pharmacokinetic data set for the period in which emesis occurred.

Note: Tables and Figures not provided that would have been in numerical order were Replicate results for 1 and 2. These figures and table did not add to the summary tables and figures provided below.

Figure S1: Mean Nisoldipine Concentration-Time Profiles after Administration of the Test Formulation 2B (Geomatrix, Treatment A) and the Reference Product (Sular, Treatment B)

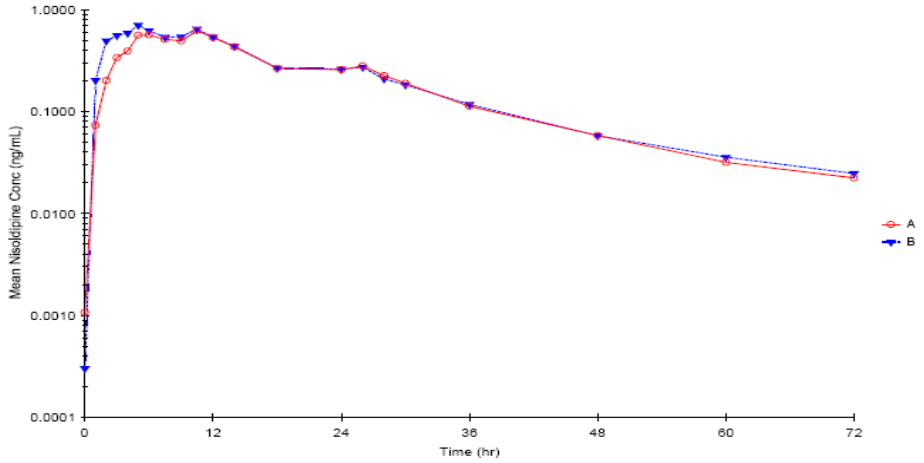


Table S4: Pharmacokinetic Parameters of Nisoldipine after Administration of the Test Formulation 2B (Geomatrix, Treatment A) and the Reference Product (Sular, Treatment B)

Parameter	Treatment A: Test Formulation 2B (Geomatrix)				Treatment B: Reference Product (Sular)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	96	8.59	4.07	47.39	94	7.35	4.12	56.04
C_{max} (ng/mL)	96	0.858	0.844	98.42	94	0.971	0.854	87.92
AUC_{last} (hr*ng/mL)	96	13.29	9.135	68.74	94	14.54	9.864	67.81
AUC_{inf} (hr*ng/mL)	96	13.80	9.435	68.37	94	15.28	10.43	68.25
AUC_{Extrap} (%)	96	3.77	3.31	87.74	94	4.46	5.69	127.74
λ_z (hr^{-1})	96	0.0530	0.0162	30.60	94	0.0494	0.0171	34.68
$T_{1/2}$ (hr)	96	14.46	4.89	33.85	94	16.53	8.54	51.67
T_{last} (hr)	96	72.00	0.00	0.00	94	72.00	0.01	0.01
C_{last} (ng/mL)	96	0.0223	0.0209	93.78	94	0.0247	0.0246	99.66

Note: Full precision data used in pharmacokinetic analysis

Table S7: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Nisoldipine Comparing the Test Formulation 2B (Geomatrix, Treatment A) to the Reference Product (Sular, Treatment B)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power
	Test	Ref	(Test/Ref)	Lower	Upper	
$ln(C_{max})$	0.7013	0.7942	88.30	81.68	95.46	0.9985
$ln(AUC_{last})$	11.5097	12.5263	91.88	86.66	97.42	1.0000
$ln(AUC_{inf})$	11.9760	13.1365	91.17	85.93	96.72	1.0000

[a] Geometric Mean for the Test Formulation 2B (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values

[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

[c] 90% Confidence Interval

SAFETY:

There were no unusual or unexpected adverse events related to the study medication. Study exit clinical laboratory, ECG, and physical examination evaluations were completed with no clinically significant findings.

The number of treatment emergent adverse events was greater in the reference formulation during period 3 and 4 (15% versus 33%). However, period 1 and 2 had similar treatment emergent adverse events between treatment groups. Headache was reported as the main adverse event in all treatment arms for both reference and test formulations. None of the adverse events were severe in nature.

CONCLUSIONS:

- The 90% confidence interval for comparing the maximum exposure, based on $ln(C_{max})$, is within the accepted 80% to 125% limits.
- The 90% confidence intervals for comparing total systemic exposure, based on $ln(AUC_{last})$ and $ln(AUC_{inf})$, are within the accepted 80% to 125% limits.
- Therefore, the test formulation, Geomatrix 2B 8.5 mg tablets, manufactured for Sciele Pharma, Inc. by SkyePharma SAS, Lyon, France, is bioequivalent to the reference product, Sular extended-release 10 mg tablets, manufactured for Sciele Pharma, Inc. by Bayer AG, Leverkusen, Germany, under fasting conditions.

REVIEWER'S COMMENT:

1. The reviewer concurs.

Study 20-093-SA – SINGLE DOSE, REPLICATE DESIGN, CROSSOVER FOOD EFFECT BIOAVAILABILITY STUDY OF NISOLDIPINE GEOMATRIX® FORMULATION 16-E ER 34 MG TABLETS.

STUDY INVESTIGATOR AND SITE: James P Doherty, DO
Cedra Clinical Research, LLC
2455 NE Loop 410, Suite 150
San Antonio, TX 78217

OBJECTIVE:

The objective of this study was to compare the rate of absorption and oral bioavailability of the test formulation, Geomatrix® 16-E 34 mg tablets (manufactured for Sciele™ Pharma, Inc. by SkyePharma SAS) when administered under fasting and fed conditions.

FORMULATION:

Geomatrix® 16-E, Nisoldipine ER 34 mg tablet (Lot #N736.15, Manuf date: 08-17-2006) Manufactured for Sciele Pharma, Inc by SkyePharma SAS.

STUDY DESIGN:

This was a single-dose, open-label, randomized, four-period, two-treatment, two-sequence, replicate design crossover study in which up to seventy-two (72) healthy male and female subjects were scheduled to receive four separate single-dose administrations of Geomatrix 16-E either after a 10-hour overnight fast or after a 10-hour overnight fast followed by a standard high-calorie, high fat breakfast meal. Each dose administration was separated by a 7-day washout period.

The subjects were admitted to the clinical research site the evening prior to each dose administration. Subjects were evaluated to ensure that they continued to meet the inclusion/exclusion and restriction criteria. Subjects were confined to the clinical research site from an appropriate time the evening prior to each dose administration to assure a minimum 10 hour fast until approximately 72 hours post dose.

For the fasting dose administrations, subjects were required to fast for at least 10 hours beginning the evening prior to dose. Each dose of study medication was administered with 240 mL of ambient temperature water. Additional water was allowed *ad lib* during the study except for 1 hour prior to dose administration through 1 hour post dose. No food was allowed for at least 4 hours after dose administration. Subjects were not permitted to lie down for 4 hours after each dose administration unless medically necessary.

For the fed dose administrations, subjects received each dose of the study medication with 240 mL of ambient temperature water after a 10-hour overnight fast followed by a standard high-calorie, high-fat breakfast. Ingestion of the standard breakfast meal began 30 minutes prior to dose. Additional water was allowed *ad lib* during the study except for 1 hour prior to dose administration through 1 hour post dose. No food was allowed for at least 4 hours after dose administration. Subjects were not permitted to lie down for 4 hours after each dose administration unless medically necessary.

Note: Breakfast was a standard high-fat FDA breakfast as recommended.

Identical standard meals (consisting of caffeine-free, xanthine-free, poppy seed-free, quinine-free and grapefruit-free foods and beverages) were served at approximately 4 and 10 hours after drug administration and at appropriate times thereafter during the in-house confinement for each study period. Only the food served was allowed during the in-house confinement period. Please refer to the Study Menu section for specifics regarding meals or meal content.

Upon completion of the in-house confinement for study periods 1, 2 and 3, subjects were reminded to continue to follow study restrictions regarding medications, tobacco, food and beverage intake, and exercise through the washout phase. They were also instructed regarding their return visits to the clinical research site.

ANALYTICAL METHODS:

Plasma samples were analyzed for nisoldipine by (b) (4) using validated LC-MS-MS procedures. The methods were validated for ranges of 0.0150 to 10.0 ng/mL and 1.00 to 100 pg/mL, based on the analysis of 0.250 mL and 1.00 mL of plasma, respectively.

Linearity:
The assay was found to be linear over the range of 0.0150 to 10.00 ng/mL with an R^2 of ≥ 0.9920.

Precision and Accuracy:
The CV% was 2.2 to 5.9 and %Bias was 4.4 to -4.3

Linearity:
The assay was found to be linear over the range of 1.0 to 100.0 pg/mL with an R^2 of ≥ 0.9923

Precision and Accuracy:
The CV% was 5.8 to 0.4 and %Bias was 2.1 to -7.0

SAMPLE COLLECTIONS AND PHARMACOKINETICS ANALYSIS:

Blood (plasma) pharmacokinetic characteristics were assessed after each dose of study medication.

Blood samples were drawn within 60 minutes prior to dose administration and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.5, 9.0, 10.5, 12.0, 14.0, 18.0, 24.0, 26.0, 28.0, 30.0, 36.0, 48.0, 60.0 and 72.0 hours after dose administration. Samples were collected under yellow light conditions in appropriately labeled, 6 mL Vacutainer tubes containing K_2-EDTA. For the pre-dose blood sample and each of the blood samples taken at 1.0 hour through 36.0 hours post-dose, 1 x 6 mL Vacutainer of blood was drawn. For the 48.0, 60.0 and 72.0 hours post-dose blood samples, 2 x 6 mL Vacutainers were drawn. The Clinical Listings section contains details on sample time collection deviations.

The following PK parameters for single dose ambrisentan dosing will be calculated for each formulation: C_{max}, T_{max}, $t_{½}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$, λ_z (apparent terminal elimination rate constant), and $t_{½}$.

Linear mixed effect model procedures and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max}, AUC_{last}, and AUC_{inf}. The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals of the log-transformed parameters were within 80% to 125%.

RESULTS:

A total of 57 subjects participated in the study with 50 subjects completing all four study periods.

Plasma concentration-time data and pharmacokinetic parameters were summarized by treatment. Mean concentration-time data are shown in Table S1 by treatment, Tables S2 and S3 by treatment within replicate (Replicate 1 = Periods 1 and 2, Replicate 2 = Periods 3 and 4), and Figures S1 through S3. Since subjects were scheduled to receive each treatment on two occasions, descriptive statistics by treatment (Table S1) are based on 98 to 103 observations.

Quantifiable pre-dose concentrations were observed for some subjects. However, since the pre-dose concentrations were well below 5% of C_{max} for these subjects after a given treatment, the pre-dose concentrations were included in all pharmacokinetic analyses without adjustment. Results of the pharmacokinetic and statistical analyses are shown below in Tables S4 through S7.

Note: Tables S1, S2, S3, S5, and S6 are not presented in this review since it did not add to the study results report. Figure S1 is only depicted since Figures S2 and S3 did not add to the study results. Figure S1 is reflective of all results found. Table S7 is also reflective of all results.

Figure S1: Mean Nisoldipine Concentration-Time Profiles after Administration of Test Formulation 16-E under Fasted (Treatment A) and Fed (Treatment B) Conditions

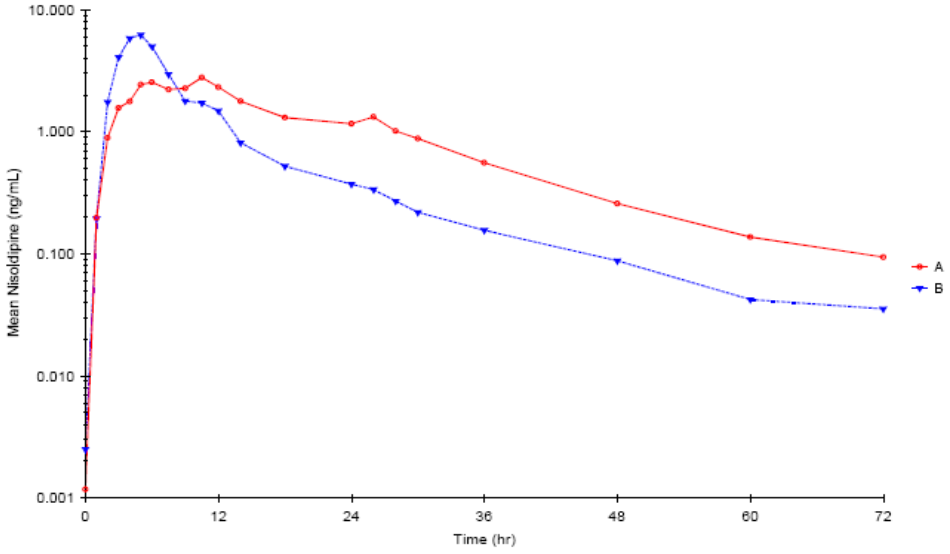


Table S4: Pharmacokinetic Parameters of Nisoldipine after Administration of Test Formulation 16-E under Fasted (Treatment A) and Fed (Treatment B) Conditions

Parameter	Treatment A: Test Formulation 16-E (Fasted)				Treatment B: Test Formulation 16-E (Fed)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	103	8.40	3.29	39.17	99	5.22	1.95	37.40
C_{max} (ng/mL)	103	3.65	1.79	48.86	99	9.76	7.16	73.36
AUC_{last} (hr*ng/mL)	103	59.93	31.20	52.07	99	48.22	27.90	57.86
AUC_{inf} (hr*ng/mL)	103	61.98	32.16	51.89	99	49.00	28.38	57.91
AUC_{Extrap} (%)	103	3.21	3.62	112.77	99	1.52	1.10	72.62
λ_z (hr^{-1})	103	0.0572	0.0149	26.03	99	0.0536	0.0139	25.99
$T_{1/2}$ (hr)	103	13.33	5.22	39.18	99	14.18	6.20	43.73
T_{last} (hr)	103	72.01	0.05	0.07	99	72.00	0.01	0.01
C_{last} (ng/mL)	103	0.0935	0.0745	79.68	99	0.0361	0.0294	81.53

Note: Full precision data used in pharmacokinetic analysis

Table S7: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Nisoldipine Comparing Test Formulation 16-E under Fasted (Treatment A) and Fed (Treatment B) Conditions

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power
	Test (Fed)	Ref (Fasted)	(Test/Ref)	Lower	Upper	
$ln(C_{max})$	8.0108	3.2686	245.08	218.61	274.77	0.9415
$ln(AUC_{last})$	42.5866	53.9429	78.95	72.76	85.66	0.9973
$ln(AUC_{inf})$	43.2364	55.7708	77.53	71.37	84.21	0.9968

[a] Geometric Mean for the Test Formulation 16-E, Fed (Test) and Fasted (Ref), based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test, Fed)/Geometric Mean (Ref, Fasted)
[c] 90% Confidence Interval

SAFETY:

There were no unusual or unexpected adverse events related to the study medication. Study exit clinical laboratory, ECG, and physical examination evaluations were completed with no clinically significant findings.

The number of treatment emergent adverse events was 55 in the fasted and 89 in the fed treatment group for periods 1 and 2. For periods 3 and 4, the number of emergent adverse events was 51 and 68 in the fasted and fed state, respectively. Headache was reported as the main adverse event in all treatment periods for both fed and fasted conditions. None of the adverse events were severe in nature.

CONCLUSIONS:

- The 90% confidence interval for comparing the maximum exposure, based on $ln(C_{max})$, is not within the accepted 80% to 125% limits.
- The 90% confidence intervals for comparing total systemic exposure, based on $ln(AUC_{last})$ and $ln(AUC_{inf})$, are not within the accepted 80% to 125% limits.
- Therefore, food has a significant effect on both the rate and extent of absorption of nisoldipine from the test formulation of Geomatrix® 16-E, 34 mg tablets manufactured for Sciele™ Pharma, Inc. by SkyePharma SAS, Lyon, France.

REVIEWER'S COMMENT:

1. The reviewer concurs.
2. The study results should be reflected in the labeling for the new formulation.

Study 20-148-SA – SINGLE DOSE FASTING, REPLICATE, CROSSOVER DESIGN COMPARATIVE BIOAVAILABILITY STUDY OF NISOLDIPINE GEOMATRIX® FORMULATION 1A EXTENDED-RELEASE 8.5 MG TABLETS VERSUS SULAR® 10 MG EXTENDED-RELEASE TABLETS.

STUDY INVESTIGATOR AND SITE: James P Doherty, DO
Cedra Clinical Research, LLC
2455 NE Loop 410, Suite 150
San Antonio, TX 78217

OBJECTIVE:

The objective of this single-dose, open-label, randomized, four-period, two-treatment, two-sequence replicate-design crossover study was to compare the rate of absorption and oral bioavailability of a test formulation, Geomatrix 1A, 8.5 mg tablets manufactured for Sciele Pharma, Inc. by SkyePharma SAS, Lyon, France, versus that of the reference product, Sular 10 mg tablets, manufactured for Sciele Pharma, Inc. by Bayer AG, Leverkusen, Germany, following an overnight fast of at least 10 hours.

FORMULATION:

Treatment A: Test Formulation 1A
Geomatrix® Nisoldipine Extended-Release
Dose = 1 × 8.5 mg tablet
Lot # P152.09
Mfg. Date: 12 February 2007
Sciele™ Pharma, Inc. (SkyePharma SAS)

Treatment B: Reference Product
Sular® Extended-Release
Dose = 1 × 10 mg tablet
Lot # C060111A
Exp. Date: 1 December 2009
Sciele™ Pharma, Inc. (Bayer AG)

STUDY DESIGN:

This was a pivotal, single-dose, open-label, randomized, four-period, two-treatment, two-sequence replicate-design crossover study in which fifty-two (52) healthy adult subjects were scheduled to receive four separate single-dose administrations of nisoldipine extended-release tablets in four study periods following an overnight fast of at least 10 hours.

Attempts were made to enroll an equal number of male and female subjects. Subjects who continued to meet inclusion/exclusion criteria the morning of dose were assigned a subject number, based on the order in which the successfully completed the screening process and procedures as outlined in the study protocol. Dosing days were separated by a washout period of at least 7 days.

Note: 34 females and 18 males were enrolled.

Subjects were required to fast for at least 10 hours beginning the evening prior to dose. Each dose of study medication was administered with 240 mL of room temperature tap water. Additional water was allowed *ad lib* during the study except for 1 hour prior to dose administration through 1 hour post dose. Subjects were not permitted to lie down for 4 hours after each dose administration unless medically necessary.

Identical standard meals (consisting of caffeine-free, xanthine-free, and grapefruit-free foods and beverages) were scheduled to be provided at 4 and 10 hours after drug administration for periods 1, 2, 3 and 4 and appropriate times thereafter. The menu for all meals and snacks consumed during research center confinement were the same for all study periods. Please refer to the Study Menu section for specifics regarding meals or meal content.

Alcohol and xanthine-containing beverages and foods (e.g., coffee, tea, cola, cocoa, chocolate) and quinine-containing products (e.g., Schweppes) were not permitted at the following times:

- From 48 hours prior to the pre-study screening until completion of screening procedures.

- At least 48 hours prior to first dose of test article until end-of-study discharge.

Poppy seed-containing food (e.g. poppy seed cake) was not allowed during the 72 hours before the pre-study examination and from 72 hours before first dose of test article until end-of-study discharge, because this could lead to a false positive result on the UDS. Foods or beverages containing grapefruit were not allowed during the entire study (14 days prior to first dose of test article until end-of-study discharge).

Upon completion of the 72-hour in-house confinement and for 4 study periods, subjects were reminded to continue to follow study restrictions regarding medications, tobacco, food and beverage intake, and exercise through the washout phase.

ANALYTICAL METHODS:

Plasma samples were analyzed for nisoldipine by CEDRA Corporation using validated LC-MS-MS procedures. The methods were validated for ranges of 0.0150 to 10.0 ng/mL and 1.00 to 100 pg/mL, based on the analysis of 0.250 mL and 1.00 mL of plasma, respectively.

Linearity:
The assay was found to be linear over the range of 0.0150 to 10.00 ng/mL with an R^2 of $\geq$ 0.9929.

Precision and Accuracy:
The CV% was 2.0 to 3.8 and %Bias was 5.3 to -3.9

Linearity:
The assay was found to be linear over the range of 1.0 to 100.0 pg/mL with an R^2 of $\geq$ 0.9970

Precision and Accuracy:
The CV% was 5.1 to 1.3 and %Bias was 3.5 to -3.0

SAMPLE COLLECTIONS AND PHARMACOKINETICS ANALYSIS:

Blood samples (1 x 6 mL, 2 x 6 mL) were collected in vacutainer tubes containing K_2-EDTA as a preservative at pre-dose (0) and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.5, 9.0, 10.5, 12.0, 14.0, 18.0, 24.0, 26.0, 28.0, 30.0, 36.0, 48.0, 60.0, and 72.0 hours after dosing during each study period.

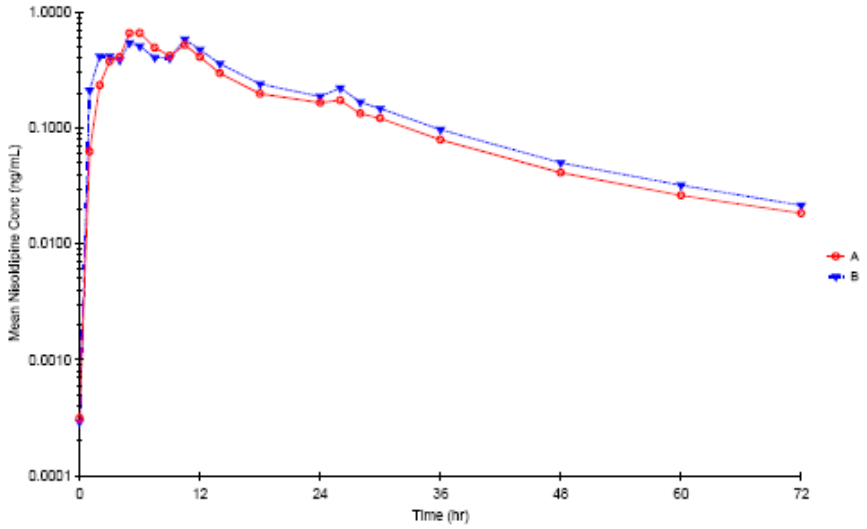
The following pharmacokinetic parameters were calculated: peak concentration in plasma (C_{max}), time to peak concentration (T_{max}), elimination rate constant (λ_z), terminal half-life ($T_{1/2}$), area under the concentration-time curve from time-zero to the time of the last quantifiable concentration (AUC_{last}), and area under the plasma concentration time curve from time-zero extrapolated to infinity (AUC_{inf}).

Linear mixed effect model procedures and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max}, AUC_{last}, and AUC_{inf}. The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals of the log-transformed parameters were within 80% to 125%.

RESULTS:

A total of 52 subjects participated in the study with 46 subjects completing all study periods Data from 50 subjects who successfully completed at least the first two or at least the last two periods of the study (one test, one reference) without protocol violation were included in the pharmacokinetic and statistical analyses. Subjects 219, 223, and 231 experienced emesis in at least one study period. Although concentration-time data were acquired and retained in the data listing, these subjects were determined to be not evaluable and were excluded from the pharmacokinetic data set for the period(s) in which emesis occurred.

Mean Nisoldipine concentration-time profiles after administration of the test formulation 1A (Geomatrix, treatment A) and the reference product (Sular, treatmentB)



NOTE: The shape of the concentration versus time curve for replicate 1 and 2 did not add anything to the summary figure above. As a result, those figures were not provided.

Pharmacokinetic parameters of Nisoldipine after administration of the Test Formulation 1A (Geomatrix, treatment A) and the reference product (Sular, treatment B)

Parameter	Treatment A: Test Formulation 1A (Geomatrix)				Treatment B: Reference Product (Sular)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	94	6.79	2.58	38.01	94	7.33	4.04	55.12
C_{max} (ng/mL)	94	0.896	0.483	53.88	94	0.806	0.454	56.34
AUC_{last} (hr*ng/mL)	94	10.68	6.098	57.08	94	11.89	5.846	49.18
AUC_{inf} (hr*ng/mL)	93	11.21	6.398	57.09	94	12.43	6.025	48.49
AUC_{Extrap} (%)	93	4.15	3.12	75.21	94	4.46	3.55	79.63
λ_z (hr^{-1})	93	0.0456	0.0143	31.44	94	0.0479	0.0146	30.48
$T_{1/2}$ (hr)	93	17.07	6.78	39.70	94	16.50	8.77	53.13
T_{last} (hr)	94	72.01	0.02	0.03	94	71.62	3.71	5.19
C_{last} (ng/mL)	94	0.0184	0.0143	77.86	94	0.0215	0.0134	62.38

Note: Full precision data used in pharmacokinetic analysis

NOTE: Tables of replicate 1 and 2 did not add anything to the summary table above. As a result, those tables were not provided.

Statisitcal analysis of the log-transformed systemic exposure parameters of Nisoldipine comparing the Test formulation (Geomatrix, treatment A) to the Reference product (Sular, treatment B)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power
	Test	Ref	(Test/Ref)	Lower	Upper	
$ln(C_{max})$	0.7716	0.7131	108.20	98.99	118.27	0.9926
$ln(AUC_{last})$	9.2423	10.6238	87.00	80.22	94.34	0.9975
$ln(AUC_{inf})$	9.6838	11.1186	87.10	80.28	94.49	0.9973

[a] Geometric Mean for the Test Formulation (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval

SAFETY:

Sitting vital signs (blood pressure, heart rate, respiration rate and temperature) were evaluated at screening and within 1 hour prior to each test article administration. After each dose administration, blood pressure and heart rate were scheduled to be measured within 5 minutes prior to each PK blood sample collection scheduled for 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.5, 9.0, 10.5, 12.0, and 14.0 hours post-dose. Additional vital sign measurements were performed as deemed medically necessary by research personnel. Blood pressure and heart rate were also measured approximately 5 minutes before PK blood samples scheduled for 24.0, 36.0, 48.0 and 72.0 hours post-dose.

There were no unusual or unexpected adverse events related to the study medication. During discharge procedures on 09 April 2007, subject 246 had abnormal urinalysis lab results for blood (25 uL), bacteria (few/HPF) and red blood cells (4-10/HPF). The subject refused to return for repeat confirmation labs. The investigator assessed these results as clinically significant resulting in an adverse event of mild microhematuria judged not related to the study drug.

Headache was reported as the main adverse event in all treatment periods. None of the adverse events were severe in nature.

CONCLUSIONS:

- The 90% confidence interval for comparing the maximum exposure, based on $\ln(C_{max})$, is within the accepted 80% to 125% limits.
- The 90% confidence intervals for comparing total systemic exposure, based on $\ln(AUC_{last})$ and $\ln(AUC_{inf})$, are within the accepted 80% to 125% limits.
- Therefore, the test formulation, Geomatrix 1A 8.5 mg tablets, manufactured for Sciele Pharma, Inc. by SkyePharma SAS, Lyon, France, is bioequivalent to the reference product, Sular extended-release 10 mg tablets, manufactured for Sciele Pharma, Inc. by Bayer AG, Leverkusen, Germany, under fasting conditions.

REVIEWER'S COMMENT:

The reviewer concurs.

APPENDIX 3 – COMPOSITIONAL TABLES
F2 SIMILARITY COMPARISONS
PROPOSED DISSOLUTION

24 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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

/s/

Lydia Velazquez
1/24/2008 07:18:37 PM
BIOPHARMACEUTICS

Patrick Marroum
1/25/2008 02:41:46 PM
BIOPHARMACEUTICS

MEMORANDUM: Clinical Pharmacology & Biopharmaceutics

NDA	20-356/019	**SUBMISSION DATE**	June 30, 2007
	019BC		October 24, 2007
	019BC		October 25, 2007
	019AZ		November 1, 2007
	019BZ		November 1, 2007
	019C		November 1, 2007
	019C		November 2, 2007
	019BB		November 2, 2007
	E-mail		November 2, 2007
	019BB		November 7, 2007
	019BC		November 16, 2007

TO: **CMC**

GENERIC NAME: Sular® (Nisoldipine Geomatrix-new formulation)
NEW DOSAGE STRENGTHS: 8.5, 17, 25.5, and 34 mg, ER oral tablets

SPONSOR: Sciele Pharma, Inc.

DIVISION OF CLINICAL PHARMACOLOGY: I
PRIMARY REVIEWER: Lydia Velazquez, Pharm.D.
TEAM LEADER: Patrick Marroum, Ph.D.

The purpose of this memo is to provide the CMC Division information regarding their consult to the Clinical Pharmacology and Biopharmaceutics Team on the above submission. The sponsor is seeking approval of a new extended release (ER) formulation for Nisoldipine (Sular®).

In an effort to improve the currently approved Sular® product, a reformulation effort was undertaken with two objectives:

1. Increase the bioavailability of orally delivered Nisoldipine while maintaining its current pharmacokinetic parameters (i.e., to create a bioequivalent formulation using less drug substance).
2. Decrease the food effect.

Sciele Pharma, Inc. intends, upon approval of this supplement, to replace all strengths of the currently approved Sular® (Nisoldipine) Extended-release Tablets (i.e., 10 mg, 20 mg, 30 mg and 40 mg) with new lower, bioequivalent strengths (i.e., 8.5 mg, 17 mg, 25.5 mg and 34 mg). The new lower strengths result from a change in formulation for each strength. Throughout this supplement, the new formulations are referred to as "Geomatrix®". A pharmacokinetics study conducted in support of this supplement demonstrated bioequivalence of the 8.5 mg Geomatrix® Tablets versus the currently approved Sular® 10 mg Tablets. Additionally, a pharmacokinetics study was conducted with the 34 mg Geomatrix® Tablets and the currently approved Sular® 40 mg Tablets, which also demonstrated bioequivalence. The resultant benefit of the bioavailability enhancement of the new Geomatrix® formulations is a 15 percent dose reduction for the patient. The secondary objective of decreasing the food effect, however, was not achieved.

The sponsor has submitted three bioequivalence studies (one for the highest and two studies for the lowest strength – formulations for the 8.5A and 8.5B mg strength) and is requesting a biowaiver for the intermediate strengths (17 and 25.5 mg). An F2 similarity comparison study has been submitted in order to seek the biowaivers. In addition, a food effect study has been submitted utilizing the highest strength as referenced above. New dissolution methods and specifications specific to the new formulation were submitted and reviewed as well.

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 20-356/019 dated June 30th, October 24th and 25th, November 1st and 2nd, 7th, and 16th, 2007 and has the following comments:

REVIEWER'S COMMENTS

1. Bioequivalence between the previous extended-release formulation (10 and 40 mg) and the new Geomatrix® formulation (8.5 and 34 mg, respectively) has been established.

2. A waiver to perform a bioequivalence study of the intermediate strengths of 17 and 25.5 mg has been granted.

3. The sponsor's revised proposed dissolution methods and specifications (different for each strength) are as follows:

USP Apparatus:	II (paddle) using stationary baskets
Speed:	50 rpm
Medium:	32.5 ± 0.1g Sodium Lauryl Sulfate in 6489 mL Purified Water containing 17.0 mL Hydrochloric Acid, pH adjusted to 1.20 ± 0.05 with Hydrochloric Acid
Volume:	900 mL
Temperature:	37º C

Q:

Proposed Dissolution Specifications

(b) (4)

The above dissolution methods are acceptable. However, the revised proposed specifications are not acceptable since:

A. A minimum of three time points is recommended to set the specifications with an early, middle, and late stage of the dissolution profile. The last time point should be the time point where at least (b) (4) % of the drug is dissolved or an asymptote has been reached. As a result, your proposed specification does not provide optimal control and does not provide sufficient discrimination within the specified time points.

B. Based on the submitted dissolution data, the final dissolution specifications should be:

		(b) (4)
Q: Strengths 8.5, 25.5, 34 mg Formulation	**4 Hours**	
	8 Hours	
	15 Hou	
Strength 17 mg Formulation	**4 Hours**	
	8 Hours	
	15 Hou	

4. The following labeling recommendations should be addressed by the sponsor:

(b) (4)

Please forward the above comments to the sponsor.

_____

_____
Lydia Velazquez, Pharm.D.
Division of Clinical Pharmacology I
Primary Reviewer

FT Initialed by Patrick Marroum, Ph.D. _____
CC list: HFD-110: NDA 20-356; HFD-860: (VelazquezL, MarroumP, MehtaM, UppoorR);
CDER Central Document Room

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/s/

Lydia Velazquez
1/2/2008 12:17:36 PM
BIOPHARMACEUTICS

Robert Kumi
1/2/2008 12:23:31 PM
BIOPHARMACEUTICS
Robert O. Kumi for Patrick Marroum

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-356/S-019

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PDUFA GOAL DATE EXTENSION

NDA 20-356/S-019

Sciele Pharma, Inc.
Attention: Ms. Allison Lowry
5 Concourse Parkway
Suite 1800
Atlanta, Georgia 30328

Dear Ms. Lowry:

Please refer to your June 30, 2007 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Sular (Nisoldipine) 8.5, 17, 25.5, and 34 mg Extended-release Tablets.

On November 1, 2007 we received your major amendment to this application. The receipt date is within two months of the user fee goal date. Therefore, we are extending the goal date by two months to provide time for a full review of the submission. The extended user fee goal date is January 2, 2008.

If you have questions, please call Denise Hinton, Regulatory Project Manager, at (301) 796-1090.

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-356/S-019

PRIOR APPROVAL SUPPLEMENT

Sciele Pharma, Inc.
Attention: Stephanie Cooke, M.S.
Director, Regulatory Affairs
Suite 1800, 5 Concourse Parkway
Atlanta, Georgia 30328

Dear Ms. Cooke:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Sular® (Nisoldipine) Extended-release Tablets

NDA Number: 20-356

Supplement number: S-019

Date of supplement: June 30, 2007

Date of receipt: July 2, 2007

This supplemental application proposes to change the formulation to lower the strength and replace all tablets (i.e., 10 mg, 20 mg, 30 mg and 40 mg) with new lower, bioequivalent strengths (i.e., 8.5 mg, 17 mg, 25.5 mg and 34 mg).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 2, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 2, 2007.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact:

Ms. Denise Hinton
Regulatory Health Project Manager
(301) 796-1090

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm

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