CLINICAL PHARMACOLOGY REVIEW

NDA: 22-029 S12	Submission Date(s): May 30, 2012
Proposed Brand Name	Salonpas Pain Relief Patch
Generic Name	10% methyl salicylate and 3% l-menthol
Reviewer	Wei Qiu, Ph. D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCPII
OND Division	DNCE
Sponsor	Hisamitsu Pharma
Relevant IND(s)	IND 62,735
Submission Type	Pediatric Efficacy Supplement
Formulation; Strength(s)	Topical Patch (10% methyl salicylate and 3% l-menthol) with size of 7 cm x 10 cm
Dosing regimen	One patch for up to 8 to 12 hours; if pain lasts after using the first patch, a second patch may be applied for up to another 8 to 12 hours. Do not use for more than 3 days in a row.
Indication	Temporarily relieves mild to moderate aches & pains of muscles & joints associated with strains, sprains, simple backache, arthritis, and bruises

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the efficacy supplement for NDA 22-029 S12 submitted on May 30, 2012, and finds it acceptable from clinical pharmacology perspective.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Salonpas (10% methyl salicylate and 3% l-menthol) pain relief patch was approved for temporarily relieves mild to moderate aches & pains of muscles & joints associated with strains, sprains, simple backache, arthritis, and bruises in adults under NDA 22-029 on February 20, 2008. The pediatric study under PREA for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises, and sprains in pediatric patients 3 to 17 years of age was deferred.

The current efficacy supplement contains completed single dose (FS-67-HP01-PK1) and multiple dose PK (FS-67-HP01-PK2), and efficacy/safety studies (FS-67-HP01-E02) in adolescents 13 to 17 years of age. Single dose and multiple dose PK of methyl salicylate, salicylic acid and menthol were adequately characterized in adolescents 13 to 17 years old following the application of the Salonpas Pain Relief Patches. Sponsor requested waiver for patients 3 to 7 and 8 to 12 years old (see Medical Officer's review for the assessment of the waiver request).

Single Dose PK in Adolescents 13 to 17 Years of Age:
In Study FS-67-HP01-PK1, a single application of two Salonpas patches (also known as FS-67 patches) for 12 hours was evaluated in 28 adolescent subjects (male and female). Concentrations of menthol, salicylic acid, and methyl salicylate were determined using

blood samples collected pre-dose and at 2, 4, 6, 8, 10, 12, 14, and 16 hours after application of the patches. Validated LC/MS/MS analytical method was used to determine salicylic acid concentration. Validated GC/MS methods were used for the determination of methyl salicylate and menthol concentrations. The LOQ values for menthol and methyl salicylate were 1 ng/mL. The assay for the determination of salicylic acid concentration had a LOQ of 30 ng/mL. The uncorrected and baseline-corrected mean plasma PK parameters are summarized in Table 1 and Table 2, respectively. The baseline levels for all three analytes were low. After application of FS-67 patches, menthol and methyl salicylate were absorbed with median tmax values ranging from 2 to 4 hours. It was not possible to accurately evaluate the gender or age differences in exposure for methyl salicylate and menthol because there were many BLQ values and many values close to the LOQ. For the same reason, AUC0-inf and t1/2 for methyl salicylate and menthol also cannot be accurately evaluated due to incomplete characterization of the terminal elimination phase.

Salicylic acid appeared in plasma with a median tmax value of 4 hrs. No obvious gender differences were observed for mean Cmax, AUC, and t1/2 values of salicylic acid. PK values were similar between 16 to 17 years old and 13 to 15 years old.

Table 1 Summary of the Mean (SD) Plasma Pharmacokinetic Parameters for Menthol, Methyl Salicylate, and Salicylic Acid from FS-67-HP01-PK1.

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
Menthol	Mean	8.39	4.00	35.7	43.6	NA	NE
	SD	17.23	(1.97, 12.0)	55.2	65.1	NA	NE
	N	28	28	26	26	0	0

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
Methyl Salicylate	Mean	14.1	2.00	70.6	81.1	NA	NE
	SD	40.1	(1.97, 16.0)	168.3	167.5	NA	NE
	N	25	25	18	18	0	0

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
Salicylic Acid	Mean	542	4.00	2900	3663	4757	3.10
	SD	236	(2.00, 9.98)	1261	1393	1288	0.71
	N	28	28	28	28	15	15

Table 2 Summary of the Mean (SD) Baseline-Corrected Plasma Pharmacokinetic Parameters for Menthol, Methyl Salicylate, and Salicylic Acid from FS-67-HP01-PK1

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
Menthol	Mean	8.24	4.00	34.3	41.8	NA	NE
	SD	17.26	(1.97, 12.0)	55.4	65.4	NA	NE
	N	28	28	26	26	0	0

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
Methyl Salicylate	Mean	13.6	2.00	72.4	77.8	NA	NE
	SD	40.2	(1.97, 16.0)	179.4	173.9	NA	NE
	N	25	25	16	17	0	0

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
Salicylic Acid	Mean	532	4.00	2823	3553	4884	2.61
	SD	239	(2.00, 9.98)	1271	1422	973	0.82
	N	28	28	28	28	13	13

Multiple Dose PK in Adolescents 13 to 17 Years of Age:

In Study FS-67-HP01-PK2, multiple applications (on 6 separate occasions) over 3 days (2 patches every 12 hours – 4 patches/day for 3 days) were evaluated in 28 adolescent subjects (male and female). PK of menthol, salicylic acid, and methyl salicylate were determined after the last application on Day 4.

Concentrations of menthol, salicylic acid, and methyl salicylate were determined using blood samples collected at baseline on Day 1 and pre-dose and at 2, 4, 6, 8, 10, 12, 14, and 16 hours after application of the patches on Day 4. Validated LC/MS/MS analytical method was used to determine salicylic acid concentration. Validated GC/MS methods were used for the determination of methyl salicylate and menthol concentrations. The LOQ values for menthol and methyl salicylate were 1 ng/mL. The assay for the determination of salicylic acid concentration had a LOQ of 30 ng/mL. The uncorrected and baseline-corrected mean plasma PK parameters are summarized in Table 3 and Table 4, respectively. The baseline levels for all three analytes were low. As the case for Study FS-67-HP-1-PK1, it was not possible to accurately evaluate the gender or age differences in exposure for methyl salicylate and menthol because there were many BLQ values and many values close to the LOQ.

No obvious gender differences were observed for mean Cmax, AUC, and t1/2 values of salicylic acid. PK values were similar between 16 to 17 years old and 13 to 15 years old.

Table 3 Summary of the Mean (SD) Plasma Pharmacokinetic Parameters for Menthol, Methyl Salicylate, and Salicylic Acid from FS-67-HP01-PK2 (Day 4)

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$t_{1/2}$ (hr)
Menthol	Mean	17.8	3.03	82.7	98.5	NA
	SD	44.3	(0, 10.0)	217.8	222.1	NA
	N	28	28	28	28	0

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$t_{1/2}$ (hr)
Methyl Salicylate	Mean	39.7	2.00	179	196	4.34
	SD	155.0	(1.98, 10.0)	633	650	NA
	N	25	25	21	21	1

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$t_{1/2}$ (hr)
Salicylic Acid	Mean	741	4.00	4065	5008	3.29
	SD	373	(1.98, 8.02)	1931	2203	1.14
	N	28	28	28	28	19

Table 4 Summary of the Mean (SD) Baseline-Corrected Plasma Pharmacokinetic Parameters for Menthol, Methyl Salicylate, and Salicylic Acid from FS-67-HP01-PK2 (Day 4)

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$t_{1/2}$ (hr)
Menthol	Mean	17.3	3.97	78.3	91.8	NA
	SD	45.3	(0, 10.0)	223.2	228.4	NA
	N	27	27	27	27	0

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$t_{1/2}$ (hr)
Methyl Salicylate	Mean	38.3	2.00	176	189	1.60
	SD	155.3	(1.98, 10.0)	651	669	NA
	N	25	25	20	20	1

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$t_{1/2}$ (hr)
Salicylic Acid	Mean	694	4.00	3722	4538	3.50
	SD	385	(1.98, 8.02)	2004	2305	1.18
	N	28	28	28	28	15

Comparison of Adolescent vs. Adults:

For a preliminary comparison, single dose PK in adolescent males following the application of 2 patches for 12 hours are compared with PK data obtained in adult males following the application of 4 patches for 8 hours from Study 67-FS-15R included in the resubmission of this NDA (see Dr. Lei Zhang's review for details). **Table 5** shows that salicylic acid, methyl salicylate and menthol exhibit lower Cmax values in adolescent males than adult males assuming PK of all analytes are dose proportional following the application of Salonpas patches. No comparison was conducted with the PK data obtained in adult males following a single application of 2 patches for 8 hours because that study FS-67-122 was not considered acceptable due to unacceptable bioanalytical method (see Dr. Lei Zhang's review for details).

Table 5 Cross Study Comparison of the Single Dose PK (baseline-corrected) in Adult Males (Study 67-FS-15R) and Adolescent Males (Study FS-67-HP01-PK1)

	Study 67-FS-15R Adult Males: 4 patches for 8 hrs (n = 12)		Study FS-67-HP01-PK1 Children 13-17 yrs Males: 2 patches for 12 hrs (n = 15)	
	Cmax (ng/mL)	AUC0-8 (ng.hr/mL)	Cmax (ng/mL)	AUC0-8h (ng.hr/mL)
Salicylic Acid	1658 (933)	11065 (5654)	530 (240)	2970 (1358)
Methyl salicylate	17.1 (15.6)	50.5 (38.6)	7.39 (13.9)*	32.2 (36.3)**
Menthol	17 (13)	91 (69)	6.02 (4.66)	29.0 (16.0)*

*n = 14; **n = 10

Validated bioanalytical methods were used for the determination of salicylic acid, methyl salicylate, and menthol concentrations in human plasma. The limit of quantification, precision, and accuracy of the analytical methods are summarized in Table 6.

Table 6 Summary of the bioanalytical method for determination of plasma salicylic acid, methyl salicylate, and menthol concentrations

Study	Analyte	Method	LLOQ	QCs	Accuracy	Precision
FS-67-HP01-PK1	Salicylic acid	LC-MS/MS	30 ng/mL	60, 200, and 1600 ng/mL	2.7% to 8.5%	2.2% to 5.5%
	Methyl salicylate	GC/MS	2 ng/mL	5, 50, and 125 ng/mL	-5.6% to 5.8%	4.0 to 12.9%
	Menthol	GC/MS	2 ng/mL	5, 50, and 125 ng/mL	-6.4% to 10.8%	6.1 to 21%
FS-67-HP01-PK2	Salicylic acid	LC/MS-MS	30 ng/mL	60, 200, and 1600 ng/mL	3.1% to 8.5%	1.5% to 4.4%
	Methyl salicylate	GC/MS	2 ng/mL	5, 50, and 125 ng/mL	0.8% to 5.4%	4.3% to 7.6%
	Menthol	GC/MS	2 ng/mL	5, 50, and 125 ng/mL	-1.6% to 9.0%	4.1% to 5.5%

2 Appendix

2.1 Filing memo

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	**22-029 S12**	**Brand Name**	**Salonpas**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**10% methyl salicylate and 3% l-menthol pain relief patch**
Medical Division	**DAAAP**	**Drug Class**	**Methyl salicylate (NSAID)**
OCP Reviewer	**Wei Qiu**	**Indication(s)**	**Temporarily relieves mild to moderate aches & pains of muscles & joints associated with strains, sprains, simple backache, arthritis, and bruises.**
OCP Team Leader	**Yun Xu**	**Dosage Form**	**Topical patch**
Date of Submission	**May 30, 2012**	**Dosing Regimen**	**One patch for up to 8 to 12 hours; if pain lasts after using the first patch, a second patch may be applied for up to another 8 to 12 hours. Do not use more than 2 patches per day. Do not use for more than 3 days in a row.**
Estimated Due Date of OCP Review	**February 3, 2013**	**Route of Administration**	**Topical**
Medical Division Due Date	**February 3, 2013**	**Sponsor**	**Hisamitsu Pharmaceutical Co.**
PDUFA Due Date	**April 3, 2013**	**Priority Classification**	**Standard**

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**	**2**		
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**x**	**2**		**One SD and one MD study**
Literature References				
Total Number of Studies		**2**		

2.2 Individual Study Synopsis

2. SYNOPSIS

NAME OF SPONSOR/COMPANY: Hisamitsu Pharmaceutical Co., Inc. NAME OF FINISHED PRODUCT: FS-67 Patch NAME OF ACTIVE INGREDIENT(S): methyl salicylate and l-menthol	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: FS-67-HP01-PK1		
Title of Study: An Open-Label Multicenter Study to Assess the Pharmacokinetic Disposition of Methyl Salicylate, Salicylic Acid, and Menthol and Safety in Adolescent Subjects Treated with a Single Application of FS-67 Patches		
Investigators: This study was conducted by 5 principal investigators.		
Study Centre(s): This study was conducted at 5 study sites in the United States.		
Publication (Reference): Not applicable		
Studied Period (years): 2009		**Phase of development:** Phase IV
Objectives: • To assess the pharmacokinetic (PK) characteristics of two (2) FS-67 patches applied as a single application by measuring concentrations of methyl salicylate, salicylic acid, and menthol in the plasma of adolescent subjects with muscle and/or joint strain, sprain, or contusion • To assess the safety of a single application of FS-67 patches in adolescent subjects with muscle and/or joint strain, sprain, or contusion		

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Hisamitsu Pharmaceutical Co., Inc. NAME OF FINISHED PRODUCT: FS-67 Patch NAME OF ACTIVE INGREDIENT(S): methyl salicylate and l-menthol	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Methodology:

This was an open-label multicenter study in adolescent subjects. Each subject was treated with a single application of FS-67 patches (application consisted of two (2) simultaneously applied patches).

Enrolled subjects had a recent history (within 6 months) or current clinical diagnosis of aches and/or pains of muscles and/or joints associated with strain, sprain, or contusion. Current strain or contusion was to have been mild to moderate in severity, and current sprain was limited to Grade 1 or 2 sprain of the ankle, wrist, knee, or elbow.

Screening assessments included medical history, physical examination, vital signs, height and weight, and clinical laboratory tests.

The single application of FS-67 patches was administered by applying two (2) FS-67 patches simultaneously on Day 1. The two (2) patches were applied to the subject's skin in close proximity to the identified qualifying injury (history of or currently diagnosed strain, sprain, or contusion). Patches were removed after 12 hours of application.

Blood samples for measurement of plasma concentrations of methyl salicylate, salicylic acid, and menthol were collected at serial time points over 16 hours on Day 1. After the collection of the 12-hour PK sample, patches were removed by study staff.

Safety assessments on Day 1 included evaluation of vital signs at baseline and at serial time points after application of the FS-67 patches, and laboratory tests and a limited physical examination after removal of the patches. The skin at the patch application site was assessed using a standard scale for skin irritation assessment at baseline and after removal of the FS-67 patches. Adverse events (AEs) were assessed throughout the 16-hour PK and safety assessment period while the subject remained at the study unit. After completion of all Day 1 assessments, subjects could be discharged from the study unit.

A follow-up telephone contact by clinical study staff was scheduled for the next day (Day 2 + 1 day) at which time any skin problems and/or other AEs observed by the subject and/or parent/guardian could be reported.

Number of Subjects (planned and analyzed):

The study was designed to enroll approximately 30 adolescent male and female subjects 13 to 17 years of age (inclusive).

A total of 28 (15 male and 13 female) subjects 13 to 17 years of age were enrolled.

Diagnosis and Main Criteria for Inclusion:

This study enrolled adolescent male and female subjects 13 to 17 years of age (inclusive) who met entry criteria and who had a recent history (within 6 months) or current clinical diagnosis of aches and/or pains of muscles and/or joints associated with strain, sprain, or contusion. Current strain or contusion was to have been mild to moderate in severity, and current sprain was limited to Grade 1 or 2 sprain of the ankle, wrist, knee, or elbow.

Test Product, Dose and Mode of Administration, Batch No.:

The test formulation was the FS-67 patch (7 cm x 10 cm). Each patch contained methyl salicylate (10%) and l-menthol (3%). Each subject received a single application of two (2) simultaneously applied FS-67 patches.

FS-67 patches used in this study were all from Batch FSA070402.

Duration of Treatment:

Two (2) FS-67 patches were applied to the skin as a single-dose application; the two (2) patches both remained applied for 12 hours on Day 1.

Reference Therapy, Dose and Mode of Administration, Batch No.:

Not applicable

Criteria for Evaluation:

Efficacy:

Not applicable

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Hisamitsu Pharmaceutical Co., Inc. NAME OF FINISHED PRODUCT: FS-67 Patch NAME OF ACTIVE INGREDIENT(S): methyl salicylate and l-menthol	Volume: Page:	

Safety:

Adverse events (AEs) were recorded throughout the study. A physical examination was performed at screening and a limited physical examination was performed on Day 1 after FS-67 patches had been removed. The skin at the patch application site was assessed by a trained evaluator using a standard scale for skin irritation assessment at baseline and after patch removal. Vital signs were measured before and at serial time points after application of the patches. Blood samples for clinical laboratory tests (chemistry and hematology panels) and a urine sample for urinalysis (dipstick) were obtained at the screening visit and again after removal of the FS-67 patches on Day 1.

Pharmacokinetics:

Concentrations of methyl salicylate, salicylic acid, and menthol in plasma were measured using blood samples collected at the following scheduled time points on Day 1: at baseline and 2, 4, 6, 8, 10, 12, 14, and 16 hours after application of the FS-67 patches.

Methyl salicylate, salicylic acid, and menthol plasma concentration results were used to derive standard PK parameters.

Statistical Methods:

Statistical analyses for safety and PK data were described in respective statistical analysis plans. Safety and PK populations were defined.

Disposition and demographic data were listed and summarized. Protocol deviations recorded on the CRF were listed and summarized. Extent of exposure analysis included the number of subjects exposed to FS-67 and the duration of exposure to FS-67 in hours. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse Evnets were listed and summarized, including a summary of the number and percentage of subjects experiencing treatment-emergent AEs (TEAEs) by system organ class (SOC) and preferred term. TEAEs were also summarized by severity and by relationship to FS-67 patch.

Laboratory test results were listed and summarized, including shift tables. Physical examination data were listed and summarized, including a shift table. Vital signs data were listed and summarized by time point.

Results of skin assessments performed using the standard scale for skin irritation assessment were listed and summarized.

PK data were analyzed using non-compartmental methods. For each subject, the following PK parameters were calculated for methyl salicylate, salicylic acid, and menthol in plasma: C_{max}, t_{max}, AUC_{0-8}, AUC_{0-12}, $AUC_{0-\infty}$, and $t_{1/2}$. Descriptive statistics were used to summarize plasma concentrations at each scheduled time point.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Not applicable

SAFETY RESULTS:

The safety population included all 28 subjects enrolled in this study. Patch exposure time was ≥ 12 hours for all subjects except 1 (11.8 hours).

Nine subjects (32.1%) had an AE. The most common TEAE was blood pressure abnormal, which occurred in 4 subjects (14.3%), and 1 other subject had a TEAE of blood pressure increased. One of the blood pressure abnormal events was considered to have a possible relationship to study drug, but all other TEAEs pertaining to blood pressure were considered to have no relationship to study drug. Variability in the blood pressure data precluded firm conclusions, but clinically meaningful effects on blood pressure directly attributable to the FS-67 patches were not discerned overall.

A TEAE of headache occurred in 2 subjects.

There was 1 subject (12/717) with a TEAE of application site erythema, considered to be moderate in intensity and to have a definite relationship to the FS-67 patches; however, no action was taken and the outcome was resolved without sequelae.

All other TEAEs occurred in only 1 subject each (injection site pain, oropharyngeal pain, and nausea). These TEAEs were considered mild and to have no relationship to study drug.

There were no deaths, no SAEs, and no AEs leading to discontinuation.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Hisamitsu Pharmaceutical Co., Inc.	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: FS-67 Patch NAME OF ACTIVE INGREDIENT(S): methyl salicylate and l-menthol	Volume: Page:	

PHARMACOKINETIC RESULTS:

After application of FS-67 patches, menthol and methyl salicylate were readily detectable for both males and females. In addition, salicylic acid readily appeared for both males and females.

No obvious sex differences in the mean C_{max} and AUC values were observed for menthol and salicylic acid. Mean C_{max} and AUC values in females were higher than those in males for methyl salicylate.

Mean C_{max} and AUC values were higher in the 16 to 17 years old group than the 13 to 15 years old group for menthol and methyl salicylate. These values were similar between the 16 to 17 years old group and the 13 to 15 years old group for salicylic acid.

Since there are many BLQ values and many values that are close to the lower limit of quantitation for a large number of sampling points, it may not be possible to accurately evaluate the sex or age differences in exposure for methyl salicylate and menthol.

The low baseline levels did not affect the pharmacokinetic assessment of the 3 analytes.

CONCLUSION:

Overall, a single application of two (2) FS-67 patches for 12 hours was considered well tolerated in the 28 adolescent subjects evaluated. No major safety concerns were identified that would preclude further evaluation of FS-67 patches in this population.

Only 3 subjects had any identified skin irritation at the patch application site: skin irritation was minimal for 2 of these subjects, and no subject had a skin irritation rating > 2.

After application of FS-67 patches, menthol and methyl salicylate were readily detectable for both males and females. In addition, salicylic acid readily appeared for both males and females. Obvious PK differences between sexes were not observed for menthol and salicylic acid, though mean C_{max} and AUC methyl salicylate values in females were higher than those in males.

The results of this study revealed no major safety concerns associated with the application of FS-67 patches in the evaluated adolescent subjects.

Date of the report: 12 January 2010

Table 11-6 Summary of the Mean (SD) Baseline-Corrected Plasma Pharmacokinetic Parameters for Menthol (63 mg) by Analyte, Gender, and Age: Day 1

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
Menthol	Mean	8.24	4.00	34.3	41.8	NA	NE
	SD	17.26	(1.97, 12.0)	55.4	65.4	NA	NE
	N	28	28	26	26	0	0
Gender		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
M	Mean	6.02	4.00	29.0	34.9	NA	NE
	SD	4.66	(2.00, 8.00)	16.0	18.1	NA	NE
	N	15	15	14	14	0	0
F	Mean	10.8	4.00	40.6	49.8	NA	NE
	SD	25.1	(1.97, 12.0)	81.2	96.0	NA	NE
	N	13	13	12	12	0	0
Age Group		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
Young	Mean	13.4	4.00	52.4	62.8	NA	NE
	SD	26.0	(1.97, 6.02)	83.2	98.3	NA	NE
	N	12	12	11	11	0	0
Younger	Mean	4.35	4.00	21.1	26.3	NA	NE
	SD	1.54	(2.00, 12.0)	9.7	11.9	NA	NE
	N	16	16	15	15	0	0

[a] Median and range (minimum, maximum) values presented for t_{max}.

Note: Young subjects are between 16 and 17 years old and younger subjects are between 13 and 15 years old.
NA = not applicable; NE = not estimated; SD = standard deviation
Source: Pharmacokinetic report Table 2 (Appendix 16.1.12.2)

Table 11-8 Summary of the Mean (SD) Baseline-Corrected Plasma Pharmacokinetic Parameters for Methyl Salicylate (210 mg) by Analyte, Gender, and Age: Day 1

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
Methyl Salicylate	Mean	13.6	2.00	72.4	77.8	NA	NE
	SD	40.2	(1.97, 16.0)	179.4	173.9	NA	NE
	N	25	25	16	17	0	0
Gender		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
M	Mean	7.39	2.00	32.2	41.1	NA	NE
	SD	13.85	(1.97, 16.0)	36.3	40.2	NA	NE
	N	14	14	10	10	0	0
F	Mean	21.5	3.97	139	130	NA	NE
	SD	59.2	(1.97, 12.0)	293	270	NA	NE
	N	11	11	6	7	0	0
Age Group		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
Young	Mean	24.3	2.00	140	132	NA	NE
	SD	57.3	(1.97, 16.0)	266	249	NA	NE
	N	12	12	7	8	0	0
Younger	Mean	3.73	2.00	19.8	29.5	NA	NE
	SD	2.57	(1.97, 12.0)	16.7	29.3	NA	NE
	N	13	13	9	9	0	0

[a] Median and range (minimum, maximum) values presented for t_{max}.
Note: Young subjects are between 16 and 17 years old and younger subjects are between 13 and 15 years old.
NA = not applicable; NE = not estimated; SD = standard deviation
Source: Pharmacokinetic report Table 4 (Appendix 16.1.12.2)

Table 11-10 Summary of the Mean (SD) Baseline-Corrected Plasma Pharmacokinetic Parameters for Salicylic Acid (210 mg) by Analyte, Gender, and Age: Day 1

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
Salicylic Acid	Mean	532	4.00	2823	3553	4884	2.61
	SD	239	(2.00, 9.98)	1271	1422	973	0.82
	N	28	28	28	28	13	13
Gender		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
M	Mean	512	4.00	2827	3452	4964	2.28
	SD	243	(2.00, 6.00)	1380	1598	1003	0.85
	N	15	15	15	15	8	8
F	Mean	555	4.00	2819	3670	4756	3.13
	SD	241	(2.00, 9.98)	1187	1242	1022	0.44
	N	13	13	13	13	5	5
Age Group		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
Young	Mean	529	4.00	2851	3474	5108	2.12
	SD	280	(2.00, 6.02)	1461	1682	838	1.08
	N	12	12	12	12	5	5
Younger	Mean	534	4.00	2803	3613	4744	2.91
	SD	213	(2.00, 9.98)	1158	1247	1078	0.45
	N	16	16	16	16	8	8

[a] Median and range (minimum, maximum) values presented for t_{max}.
Note: Young subjects are between 16 and 17 years old and younger subjects are between 13 and 15 years old.
SD = standard deviation
Source: Pharmacokinetic report Table 6 (Appendix 16.1.12.2)

2. SYNOPSIS

NAME OF SPONSOR/COMPANY: Hisamitsu Pharmaceutical Co., Inc. NAME OF FINISHED PRODUCT: FS-67 Patch NAME OF ACTIVE INGREDIENT(S): methyl salicylate and l-menthol	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: FS-67-HP01-PK2		
Title of Study: An Open-Label Multicenter Study to Assess the Pharmacokinetic Disposition of Methyl Salicylate, Salicylic Acid, and Menthol and Safety in Adolescent Subjects Treated with Multiple Applications of FS-67 Patches		
Investigators: This study was conducted by 5 principal investigators.		
Study Centre(s): This study was conducted at 5 study sites in the United States.		
Publication (Reference): Not applicable		
Studied Period (years): 2009		**Phase of development:** Phase IV
Objectives: • To assess the pharmacokinetic (PK) characteristics of multiple applications of FS-67 patches by measuring concentrations of methyl salicylate, salicylic acid, and menthol in the plasma of adolescent subjects with muscle and/or joint strain, sprain, or contusion • To assess the safety of a multiple applications of FS-67 patches in adolescent subjects with muscle and/or joint strain, sprain, or contusion		

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Hisamitsu Pharmaceutical Co., Inc. NAME OF FINISHED PRODUCT: FS-67 Patch NAME OF ACTIVE INGREDIENT(S): methyl salicylate and l-menthol	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Methodology:

This was an open-label multicenter study in adolescent subjects. Subjects were treated with multiple applications of FS-67 patches. The study was designed to enroll approximately 30 male and female adolescents 13-17 years of age.

Enrolled subjects had a recent history (within 6 months) or current clinical diagnosis of aches and/or pains of muscles and/or joints associated with strain, sprain, or contusion. Current strain or contusion was to have been mild to moderate in severity, and current sprain was limited to Grade 1 or 2 sprain of the ankle, wrist, knee, or elbow.

Following informed consent and assent, subjects underwent standard screening assessments within 1 week before receiving the first application (Application # 1) of FS-67 patches. Subsequently, study site visits occurred on Day 1 (including baseline assessments and initiation of treatment with FS-67 patches) and Day 4 (final FS-67 patches applied and removed).

Subjects received multiple applications (on 6 separate occasions) of FS-67 patches over approximately 3 days (starting on Day 1 and continuing through Day 4). Each application consisted of two (2) FS-67 patches applied simultaneously to the skin in close proximity to the identified qualifying injury (history of or currently diagnosed strain, sprain, or contusion). For each application, patches remained applied to the skin for 12 hours and were then to have been removed.

Application # 1 patches were applied on Day 1 while the subject was at the study site. Subsequent applications (Application # 2 through Application # 5) of FS-67 patches were applied by the subject or parent/guardian at home once every 12 hours over the next 2 consecutive days (Day 2 and Day 3). The final FS-67 patches (Application # 6) were applied on Day 4 when the subject returned to the study site.

On Day 4, subjects remained at the study site for approximately 16 hours after the Application # 6 patches were applied. After 12 hours of application, Application # 6 patches were removed.

Pharmacokinetic blood samples for measurement of concentrations of methyl salicylate, salicylic acid, and menthol in plasma were collected at baseline on Day 1 and at defined serial time points on Day 4 before and after application of Application # 6 patches.

Safety evaluations included physical examinations, clinical laboratory testing, vital signs measurements, AE assessments, and skin irritation assessments.

After completion of the 16-hour PK and safety assessments on Day 4, subjects could be discharged from the study site to home.

On Day 2 and Day 3, a study staff member contacted subjects (and/or parents/guardians) by telephone to obtain information regarding the patch application site condition and to inquire about any AEs. On Day 5 (+ 1 day), a study staff member again contacted subjects (and/or parents/guardians) by telephone for follow-up to obtain information regarding the patch application site condition and any AEs.

Number of Subjects (planned and analyzed):

The study was designed to enroll approximately 30 adolescent male and female subjects 13 to 17 years of age.

A total of 29 subjects (14 male and 15 female) were enrolled.

Diagnosis and Main Criteria for Inclusion:

This study enrolled adolescent male and female subjects 13 to 17 years of age (inclusive) who met entry criteria and who had a recent history (within 6 months) or current clinical diagnosis of aches and/or pains of muscles and/or joints associated with strain, sprain, or contusion. Current strain or contusion was to have been mild to moderate in severity, and current sprain was limited to Grade 1 or 2 sprain of the ankle, wrist, knee, or elbow.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Hisamitsu Pharmaceutical Co., Inc. NAME OF FINISHED PRODUCT: FS-67 Patch NAME OF ACTIVE INGREDIENT(S): methyl salicylate and l-menthol	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Test Product, Dose and Mode of Administration, Batch No.:

The test formulation was the FS-67 patch (7 cm x 10 cm). Each patch contained methyl salicylate (10%) and l-menthol (3%).

FS-67 patches were applied to the skin twice a day over approximately 3 days. Each patch application consisted of two (2) simultaneously applied FS-67 patches. Each subject was to have received a total of 6 applications (total of 12 patches overall) during the study.

On Day 1, the first patches (Application #1) were applied. Subsequent patches (Application # 2 through Application # 5) were applied once every 12 hours on Day 2 through Day 3 while subjects were at home. For each patch application, patches were to have remained applied to the skin during the 12-hour application interval and were then to have been removed. The final patches (Application # 6) were applied at the study site on Day 4 and were removed after 12 hours of application.

FS-67 patches used in this study were all from Batch FSA070402.

Duration of Treatment:

FS-67 patches were applied to the skin twice a day for up to 72 hours. Each patch application consisted of two (2) simultaneously applied FS-67 patches. Each subject received a total of six (6) applications (total of 12 patches overall) during the study.

Reference Therapy, Dose and Mode of Administration, Batch No.:

Not applicable

Criteria for Evaluation:

Efficacy:

Not applicable

Safety:

Safety evaluations included physical examinations, clinical laboratory testing, vital signs measurements (blood pressure, pulse rate, and body temperature), AE assessments, and skin irritation assessments.

Screening assessments included review of medical history, physical examination, measurement of vital signs and height and weight, and clinical laboratory tests of blood and urine.

Physical examinations were performed at the screening visit and after removal of the final patches on Day 4. Weight was measured at the screening and Day 4 visits; height was measured at the screening visit.

Clinical laboratory tests of blood (chemistry and hematology panels) and urine (urinalysis) were performed using samples obtained at the screening visit and after removal of the final patches on Day 4. Blood samples for serology testing were obtained at the screening visit only. A urine drug screen and a breath alcohol test were performed at the screening visit and again before application of the first patches on Day 1. A blood sample for serum pregnancy test (females only) was obtained at the screening visit, and a urine pregnancy test (females only) was performed on Day 1 and on Day 4.

Vital signs were measured at the screening visit, on Day 1 (before and approximately 1 hour after initial application of Application # 1 patches), and on Day 4 (before and at serial time points after initial application of Application # 6 patches).

Adverse events were assessed throughout the study (starting at baseline on Day 1 and continuing through the follow-up telephone contact).

The patch application site was evaluated by study staff on Day 1 (baseline) and on Day 4 (after removal of Application # 5 and Application # 6 patches). At these times, a trained evaluator used a standard scale for skin irritation assessment. Skin irritation ratings ≥ 2 on Day 4 were to have been reported as AEs. The patch application site was observed by the subject (or parent/guardian) at home on Day 2 and Day 3, as well as on Day 5.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Hisamitsu Pharmaceutical Co., Inc. NAME OF FINISHED PRODUCT: FS-67 Patch NAME OF ACTIVE INGREDIENT(S): methyl salicylate and l-menthol	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Pharmacokinetics:

Concentrations of methyl salicylate, salicylic acid, and menthol in plasma were measured using blood samples collected at baseline on Day 1 and subsequently at the following scheduled time points on Day 4: before and 2, 4, 6, 8, 10, 12, 14, and 16 hours after initial application of Application # 6 patches.

Methyl salicylate, salicylic acid, and menthol concentration in plasma results were used to derive standard PK parameters.

Statistical Methods:

Statistical analyses for safety and PK data were described in respective statistical analysis plans. Safety and PK populations were defined.

Disposition and demographic data were listed and summarized. Protocol deviations recorded on the case report form were listed and summarized. Extent of exposure analysis included the number of subjects exposed to FS-67 and the duration of exposure to FS-67 in hours. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse Events were listed and summarized, including a summary of the number and percentage of subjects experiencing treatment-emergent AEs (TEAEs) by system organ class (SOC) and preferred term. TEAEs were also summarized by severity and by relationship to FS-67 patch. Serious AEs (SAEs) and AEs leading to discontinuation were summarized and listed. Adverse events defined as related to the patch location were summarized.

Laboratory test results were listed and summarized, including shift tables for chemistry and hematology tests. Physical examination data were listed and summarized, including a shift table. Vital signs data were listed and summarized by time point.

Results of skin assessments performed using the standard scale for skin irritation assessment were listed and summarized.

PK data were analyzed using non-compartmental methods. For each subject, the following PK parameters were calculated for methyl salicylate, salicylic acid, and menthol in plasma: C_{max}, t_{max}, AUC_{0-8}, AUC_{0-12}, and $t_{1/2}$. Descriptive statistics were used to summarize the PK data.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Not applicable

Table 11-6 Summary of the Mean (SD) Baseline-Corrected Plasma Pharmacokinetic Parameters for Menthol (63 mg) by Analyte, Gender, and Age: Day 4

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$t_{1/2}$ (hr)
Menthol	Mean	17.3	3.97	78.3	91.8	NA
	SD	45.3	(0, 10.0)	223.2	228.4	NA
	N	27	27	27	27	0
Gender		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$t_{1/2}$ (hr)
M	Mean	27.3	3.98	119	135	NA
	SD	62.1	(0, 10.0)	309	315	NA
	N	14	14	14	14	0
F	Mean	6.58	2.10	35.0	45.3	NA
	SD	4.91	(2.00, 8.02)	29.0	36.1	NA
	N	13	13	13	13	0
Age Group		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$t_{1/2}$ (hr)
Young	Mean	6.79	4.00	31.8	41.5	NA
	SD	4.78	(0, 8.02)	20.5	27.5	NA
	N	13	13	13	13	0
Younger	Mean	27.1	2.00	121	138	NA
	SD	62.2	(1.98, 10.0)	308	314	NA
	N	14	14	14	14	0

[a] Median and range (minimum, maximum) values presented for t_{max}.

Note: Young subjects are between 16 and 17 years old and younger subjects are between 13 and 15 years old.

NA = not applicable; SD = standard deviation

Source: Pharmacokinetic report Table 2 (Appendix 16.1.12.2)

Table 11-8 Summary of the Mean (SD) Baseline-Corrected Plasma Pharmacokinetic Parameters for Methyl Salicylate (210 mg) by Analyte, Gender, and Age: Day 4

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$t_{1/2}$ (hr)
Methyl Salicylate	Mean	38.3	2.00	176	189	1.60
	SD	155.3	(1.98, 10.0)	651	669	NA
	N	25	25	20	20	1
Gender		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$t_{1/2}$ (hr)
M	Mean	70.9	2.00	391	416	1.60
	SD	224.3	(1.98, 10.0)	1030	1057	NA
	N	12	12	8	8	1
F	Mean	8.20	2.00	31.6	36.9	NA
	SD	7.77	(1.98, 4.00)	19.5	19.8	NA
	N	13	13	12	12	0
Age Group		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$t_{1/2}$ (hr)
Young	Mean	4.62	2.00	25.4	34.8	NA
	SD	2.24	(2.00, 8.00)	9.0	10.0	NA
	N	11	11	8	8	0
Younger	Mean	64.8	2.00	276	291	1.60
	SD	206.9	(1.98, 10.0)	839	863	NA
	N	14	14	12	12	1

[a] Median and range (minimum, maximum) values presented for t_{max}.
Note: Young subjects are between 16 and 17 years old and younger subjects are between 13 and 15 years old.
NA = not applicable; SD = standard deviation
Source: Pharmacokinetic report Table 4 (Appendix 16.1.12.2)

Table 11-10 Summary of the Mean (SD) Baseline-Corrected Plasma Pharmacokinetic Parameters for Salicylic Acid (210 mg) by Analyte, Gender, and Age: Day 4

Analyte		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$t_{1/2}$ (hr)
Salicylic Acid	Mean	694	4.00	3722	4538	3.50
	SD	385	(1.98, 8.02)	2004	2305	1.18
	N	28	28	28	28	15
Gender		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$t_{1/2}$ (hr)
M	Mean	657	3.98	3583	4335	3.71
	SD	334	(1.98, 6.02)	1712	1898	1.09
	N	14	14	14	14	7
F	Mean	730	4.00	3861	4741	3.32
	SD	439	(2.00, 8.02)	2316	2709	1.29
	N	14	14	14	14	8
Age Group		C_{max} (ng/mL)	t_{max}[a] (hr)	AUC_{0-8} (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	$t_{1/2}$ (hr)
Young	Mean	630	4.00	3406	4251	3.84
	SD	357	(2.00, 8.02)	1932	2159	1.41
	N	13	13	13	13	8
Younger	Mean	749	3.97	3995	4787	3.12
	SD	411	(1.98, 6.00)	2090	2471	0.77
	N	15	15	15	15	7

[a] Median and range (minimum, maximum) values presented for t_{max}.
Note: Young subjects are between 16 and 17 years old and younger subjects are between 13 and 15 years old.
SD = standard deviation
Source: Pharmacokinetic report Table 6 (Appendix 16.1.12.2)

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