CLINICAL REVIEW

Application Type	**NDA**
Application Number(s)	**22-029 S12**
Priority or Standard	**Standard**
Submit Date(s)	**May 30, 2012**
Received Date(s)	**June 3 and 29, 2012**
PDUFA Goal Date	**March 29, 2013**
Division / Office	**DAAAP / ODE II**
Reviewer Name(s)	**Christina Fang, M.D., M.P.H.**
Review Completion Date	**February 23, 2013**
Established Name	**10% methyl salicylate and 3% l-menthol patch**
(Proposed) Trade Name	**Salonpas® Pain Relief Patch**
Therapeutic Class	**External analgesics**
Applicant	**Hisamitsu Pharmaceutical Co., Inc**
Formulation(s)	**Topical patch**
Dosing Regimen	**One patch to affected area for up to 8-12 hours, not >2 patches per day or use for >3 days in a row**
Indication(s)	**Temporarily relieves mild to moderate aches & pains of muscles & joints associated with strains, sprains, simple backache, arthritis, and bruises**
Intended Population(s)	**Adolescent OTC population**

Template Version: March 6, 2009

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1.1 Recommendation on Regulatory Action

The use of Salonpas patch for external pain in adolescents aged 13 to 17 years is not recommended based on the results of the efficacy study.

1.2 Risk Benefit Assessment

The benefit for the use of Salonpas patch for external pain in adolescents aged 13 to 17 years has not been demonstrate [redacted] (b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Refer to the NDA review by Dr. Ryan Raffaelli.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

Refer to the NDA review by Dr. Ryan Raffaelli.

2.1 Product Information

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Refer to the NDA review by Dr. Ryan Raffaelli.

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

There are no significant efficacy issues related to other review disciplines. Refer also to the NDA review by Dr. Ryan Raffaelli.

4.1 Chemistry Manufacturing and Controls

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Table 1 List of Efficacy Study

Protocol # # of sites	Study Design	Dates of Study	Treatment group and dosing	N	Mean age/range Gender Race	Data relevance
FS-67-HP01-E02 26 sites	Multiple-dose, randomized, double-blind, placebo-controlled study of ankle sprain	12/09 to 10/10	FS-67 patch Placebo patch One patch of eight-hour application every 12 hours for up to 3 days	126 126	15 (13-17) years 152 Male/100 Female 188 White/41 Black/ 23 other	Efficacy

5.2 Review Strategy

There is one efficacy study submitted in the NDA. This was reviewed and the review covers the efficacy-related main components of the protocol, baseline characteristics, study conduct, and efficacy results.

5.3 Discussion of Individual Studies/Clinical Trials

Protocol
Study FS-67-HP01-E02 was planned as a multiple-center, randomized, double-blind, placebo-controlled, parallel group, multiple-dose (6 patches in 3 days with both single- and multiple-patch evaluation) study of FS-67 patch (10% methyl salicylate and 3% 1-menthol) in adolescents with painful ankle sprain.

Eligible subjects were planned to include male and non-pregnant female adolescents 13 to 17 years of age with a clinical diagnosis of painful acute benign unilateral Grade 1 or 2 ankle sprain of the lateral ligament(s), ankle injury that occurred within 72 hours, and resting pain intensity (PI) of 50-85 mm (inclusive) on the 100 mm Visual Analog Scale (VAS) with higher PI score upon weight bearing than the resting PI at screening and baseline (Day 1 before application of Patch 1). The main exclusion criteria planned were Grade 3 ankle sprain, inability to perform required weight-bearing assessments, ankle sprain due to multiple injuries or bone fracture within the past 6 months, lack of any visible signs of ankle sprain, symptoms attributable to primary inflammatory diseases of the joint, and symptoms attributable to dermatitis near the area of patch application.

Subjects meeting all the inclusion and exclusion criteria were planned to be randomly assigned to a treatment group to receive either a FS-67 patch (105 mg methyl salicylate and 31.5 mg 1-menthol) or a placebo patch. The treatment patch (7 cm by 10 cm) was planned to be applied to the skin at the affected area of greatest pain for eight hours. Subjects were planned to be discharged home after the removal of the initial patch. The schedule for subsequent 8-hour patch

application was planned to include Patch 2 within the time interval of 8.5-12 hours based on the need for remedication, Patch 3 at 24 hours, and then a patch every 12 hours for a total of 6 patches (including the initial patch). The blind was planned to be maintained by use of an odor-masking spray applied to all patches before dispensing to patients.

Efficacy data planned to be collected included pain intensity scores using the 100-mm VAS at rest (5-minute rest) and upon weight bearing (monopodal weight bearing for 1 second) at baseline, and at 1, 2, 4, 6, 8 (on site), 10 and 12 hours (off site) after the initial patch and 15 minutes before application and 15 minutes after removal of each subsequent patch.

The primary efficacy endpoint was planned to be the summed pain intensity difference score through eight hours (SPID8) for pain upon weight bearing. Secondary efficacy endpoints were planned to include SPID8 at rest, PID8, SPID12, SPID20, SPID44, and SPID68 upon weight bearing and at rest, time to application of remedication (Patch 2), and time to administration of rescue medication. The planned exploratory efficacy endpoints included PID2, PID4, PID6, PID10, PID12, SPID32, SPID56, and SPID72 upon weight bearing and at rest.

Statistical highlights
The statistical methodology and analysis plan and related changes are presented and discussed in detail in the statistical review. Some points are mentioned below for clarification purposes.

Sample population for efficacy analysis
The sample population for primary analysis was planned to be the modified intent-to-treat (mITT) population, which included all subjects who signed a written informed consent/assent and were randomized and treated with at least one patch with a baseline and at least one post-baseline PI assessment upon weight bearing.

Analysis
Continuous efficacy variables such as SPID and PID were planned to be analyzed by using analysis of variance (ANOVA) model with treatment as a fixed effect and pain intensity at baseline as a covariate.

Missing data management
The planned imputation for missing data included the following:

- WOCF for discontinuation due to reasons other than no pain
- LOCF for discontinuation due to no more pain from injured ankle or taking rescue

Previous reviews of the protocol
The protocol was submitted to IND 62,735 as a Special Protocol Assessment on August 26, 2009 and was reviewed by this reviewer (clinical review dated October 14, 2009 in DARRTS) and statistical reviewer Dr. Yongman Kim (dated October 6, 2009 in DARRTS).

Protocol amendments

There were three protocol amendments, including Amendment 1 submitted on March 12, 2010, Amendment 2 submitted on March 25, 2010, and Amendment 3 submitted on May 19, 2010). The revisions were summarized by the Applicant as below (quoted from the NDA submission).

Protocol Amendment 1

- In the synopsis methodology section, the duration of treatments was updated to indicate that after removal of Patch 1 on Day 1, subjects were to be discharged from the clinic.
- Time intervals were added to specified time points for study assessments in the synopsis.
- Safety evaluations were updated to include vital signs during screening, after removal of
- Patch 1, and on Day 4. Skin irritation assessment was also included after Patch 1 removal on Day 1.
- The overall study design section was revised and pain intensity assessments at Day 1 at clinic and at home was elaborated upon.
- The time between Patch 2 application/removal and Patch 3 application in Figure 1 in overall study design was updated.
- The length of stay at the study site on Day 1 was reduced from 12-14 hours to 9 hours.
- Patch 1 removal and additional observations and procedures were updated accordingly.
- Day 1 outpatient procedures and assessments were added accordingly.
- Prohibited medications and substances information was revised.

Protocol Amendment 2

- Test was added to clarify VAS assessment completion by the subject at home.
- Medications and therapies used within 2 hours before baseline pain assessments were included in the prohibited medications; previously it had been 6 hours.
- Other prohibited therapies included massage, stretching, compression, clasps, bands, splints, casts, or other supports. Conditions for use of crutches were included.
- Day 1 outpatient procedures and assessments were updated and it was added that before rescue medication was administered, a VAS pain intensity assessment was to be performed.
- Criteria for early discontinuation of patch application and study participation information was updated and description of notebook entries were updated to include skin irritations, AEs, concomitant medications and rescue medication records.
- Missing data and imputation methods were updated
- Prohibited medications, substances, and other therapies information were updated to describe amphetamines, methylphenidate, and/or other stimulants.

Protocol Amendment 3

- In the inclusion criteria, time to ankle sprain injury was updated to be occurred within 72 hours of the day on which baseline assessments and application of Patch 1 occur. In the previous version of the protocol, it had been 48 hours.
- Day 1 outpatient procedures and assessments information was updated and the conditions for application of additional patches and pain intensity VAS assessments were clarified, and continuation of skin assessments evaluation was added.

Table 2 Protocol

Study #	**FS-67-HP01-E02**
Objectives	To study efficacy and safety of the methyl salicylate and 1-menthol combination patch in adolescents with painful ankle sprain
Design	Multiple-center (26 U.S. sites), randomized, double-blind, placebo-controlled, parallel, multiple-dose (6 patches in 3 days with both single- and multiple-patch evaluation)
Sample population	Adolescents age 13 to 17 years with painful acute benign unilateral Grade 1 or 2 ankle sprain of the lateral ligament(s) within 72 hours and PI at rest of 50 mm to 85 mm (inclusive) VAS score at screening and at baseline (refer to eligibility criteria in Appendix at the end of this section for detail)
Baseline	PI of 50 mm to 85 mm at rest and PI upon monopodal weight bearing higher than the corresponding score at rest, both at screening and at baseline
Treatment	Salonpas Patch (7x10cm) or a matching placebo patch to be applied for 8 ± 0.5 hours q12 hours for a total of 6 patches Patch 1: at Hour 0 Patch 2: to be applied upon request in the time interval of 8.5 to 12 hours after Patch 1 Patch 3: to be applied at Hour 24 (±0.5 hours) after Patch 1 Subsequent patches (Patch 4, 5, and 6) to be applied at 12-hour intervals after Patch 3
Rescue	Acetaminophen (suggested waiting time of 2 hours after the initial patch) 500 mg q4-6 hours and not to >1500 mg in 24 hours Missing data imputation after rescue
Concomitant medication	Prohibited: Analgesics and other treatments that could confound assessment of analgesic response such as NSAIDs, acetaminophen (unless used as rescue), and opioid containing products, tricyclic antidepressants, antihistamines (sedating), tranquilizers, hypnotics, sedatives, drugs with potential for abuse, topical agents, any type of cryotherapy Allowed: Concomitant medication for coexisting diseases that are unlikely to affect the study assessments, standard-of-care procedures such as rest and elevation, crutches (except during pain assessment)
Efficacy data	PI at rest and upon weight bearing at 1, 2, 4, 6, 8 (on site), 10, and 12 hours (off site) after application of Patch 1, 15 minutes before application and 15 minutes after removal of each subsequent patch
Efficacy parameter	**Primary efficacy endpoint:** SPID8 upon weight bearing **Secondary efficacy endpoints** . SPID8 at rest . PID8, SPID12, SPID20, SPID44, SPID68 upon weight bearing and at rest . Time to application of remedication (Patch 2) . Time to administration of rescue medication **Exploratory efficacy endpoints** . PID2, PID4, PID6, PID10, PID12 . SPID32, SPID56, SPID72 upon weight bearing and at rest

Results

Demographic and other baseline characteristics

The study population consisted of 252 adolescents aged 13 to 17 years who received study patch applications with a mean age of 15 years, 75% Caucasian, 16% African American, and 40% female. The treatment groups were approximately balanced with regard to demographic characteristics such as age, gender, race, ethnicity, height, and weight and with regard to the baseline pain intensity, about 65 mm (on 100 mm VAS scale) for pain at rest and 75 mm for pain upon weight bearing (refer to the table below).

Table 3 Demographics and Baseline Characteristics

Demographic/Statistics	**FS-67 (N = 126)**	**Placebo (N = 126)**	**Study population (N = 252)**
Age (years)			
Mean (Standard Deviation)	15.0 (1.38)	15.3 (1.34)	15.2 (1.36)
Median	15.0	16.0	
Minimum-Maximum	13-17	13-17	13-17
Gender, n (%)			
Male	75 (59.5)	77 (61.1)	152 (60.3)
Female	51 (40.5)	49 (38.9)	100 (39.7)
Race, n (%)			
Caucasian	97 (77.0)	91 (72.2)	188 (74.6)
Black or African American	18 (14.3)	23 (18.3)	41 (16.3)
Asian	3 (2.4)	3 (2.4)	6 (2.4)
European/Middle Eastern	1 (0.8)	1 (0.8)	2 (0.8)
Native Hawaiian or Pacific Islander	0 (0.0)	1 (0.8)	1 (0.4)
Other	7 (5.6)	7 (5.6)	14 (5.6)
Ethnicity, n (%)			
Hispanic or Latino	71 (56.3)	68 (54.0)	139 (55.2)
Not Hispanic or Latino	55 (43.7)	58 (46.0)	113 (44.8)
Height (cm)			
Mean (Standard Deviation)	166.3 (10.0)	168.5 (11.1)	
Median	165.1	167.6	
Minimum-Maximum	131.0- 189.0	134.0 - 200.0	
Weight (kg)			
Mean (Standard Deviation)	69.2 (21.2)	70.5 (17.7)	
Median	64.3	65.3	
Minimum-Maximum	36.0-157.0	40.6-127.3	
Baseline Pain Intensity			
At rest	64.2	65.0	64.6
Upon weight bearing	74.2	75.6	74.9

Source: Tables 11-2, 11-3, and 11-5 on pages 57-61 of the study report.

Patient disposition and efficacy sample

A total of 252 patients were treated with the study patches and 250 patients completed the study. The explanations for two cases of dropouts in the FS-67 group were problems with patch adherence in one patient and unknown in the second patient as shown in the table below. About 40% of the study population, 50 patients in the FS-67 group and 52 patients in the placebo group, discontinued the use of patches early due to pain resolution (refer to the Table 10-3 on page 52 of the study report). They were not considered dropouts.

The mITT population for efficacy analysis included all 252 patients who received patch treatment. Although the acceptable mITT definition for the primary efficacy analysis is generally all patients randomized who received at least one dose of study drug, regardless of baseline or later pain measurements, the inclusion of all 252 randomized patients makes the analysis population appropriate and acceptable.

Table 4 Patient Disposition

	FS-67	Placebo
Number of subjects treated	126	126
Number of subjects completed	124	126
Number of subjects who discontinued early	2	0
Adverse event	0	0
Other	2	0
Patch non adherence	1	0
Unknown	1	0

Source: Tables 10-1 and 10-2 on pages 51-52 and Appendix 16.2.1.1 on pages 1435-1455 of the study report.

Protocol deviations

Protocol deviations were reported in 16 (12.7%) patients in the FS-67 group and 15 (11.9%) in the placebo group mostly due to deviations from inclusion criteria in terms of the baseline pain intensity (PI) such as PI at rest either < 50 mm or >85 mm or higher than PI upon weight bearing as summarized in the table below.

Table 5 Protocol Deviation

	FS-67 N=126	Placebo N=126
Violation of eligibility criteria	15	14
Baseline PI at rest <50 mm	3	3
Baseline PI at rest >85 mm	4	5
Baseline PI at rest > PI upon weight bearing	7	4
Met Exclusion Criterion 30	1	0
Met Exclusion Criterion 5	0	1
Not met Inclusion Criteria 8	0	1
Prohibited treatment (containing menthol)	1	0
Rescue time violation	0	2

Total	*16*	*15*

Source: Tables 10.4 and 10.5 on pages 53-54 and Appendix 16.2.2.2 on pages 1501-1507 of the study report.

Efficacy results

The results of analysis using mITT population and WOCF to impute missing data are reviewed here.

Primary efficacy endpoint
The result of the primary efficacy analysis revealed that, at the end of 8-hour patch application, the LS mean difference in SPID (VAS) upon weight bearing between the FS-67 and placebo patch groups was 18.1 (107.2 for the FS-67 group versus 89.1 for the placebo group), a very small difference which was not statistically significant.

Table 6 Primary Efficacy Endpoint: SPID8 upon Weight Bearing

	Statistic	**FS-67 N=126**	**Placebo N=126**	**Difference in LS (FS-67/Placebo)**
Raw Data	Mean	106.349	93.760	
	(Standard Deviation)	(103.6344)	(108.7606)	
	Standard Error Mean	9.2325	9.6892	
	Median	70.750	62.250	
	Minimum	-61.50	-125.63	
	Maximum	390.00	447.00	
Analysis of Covariance	LS Mean (SE) [a]	107.19	89.13	18.06
	Standard Error Mean	9.05	9.42	
	(95% Confidence Interval)	(89.4, 125.0)	(70.6, 107.7)	(-5.8, 41.9)
	P-value			0.137

[a] The least-squares estimate was adjusted for baseline pain intensity visual analog scale score and pooled treatment center.
Source: Table 11-9 on page 68 of the study report.

Other efficacy endpoints (secondary and exploratory endpoints)
Most efficacy endpoints (except time to remedication and time to rescue) were either time-specific PID or summed PID (SPID) up to a specified time point and thus, are grouped together under the two categories: PID and SPID.

Time-specific PID
Time-specific PID scores are summarized in the table and four graphs below: PID at rest from 0 to 12 hours, PID upon weight bearing from 0 to 12 hours, PID at rest from 0 to 72 hours, and PID upon weight bearing from 0 to 72 hours.

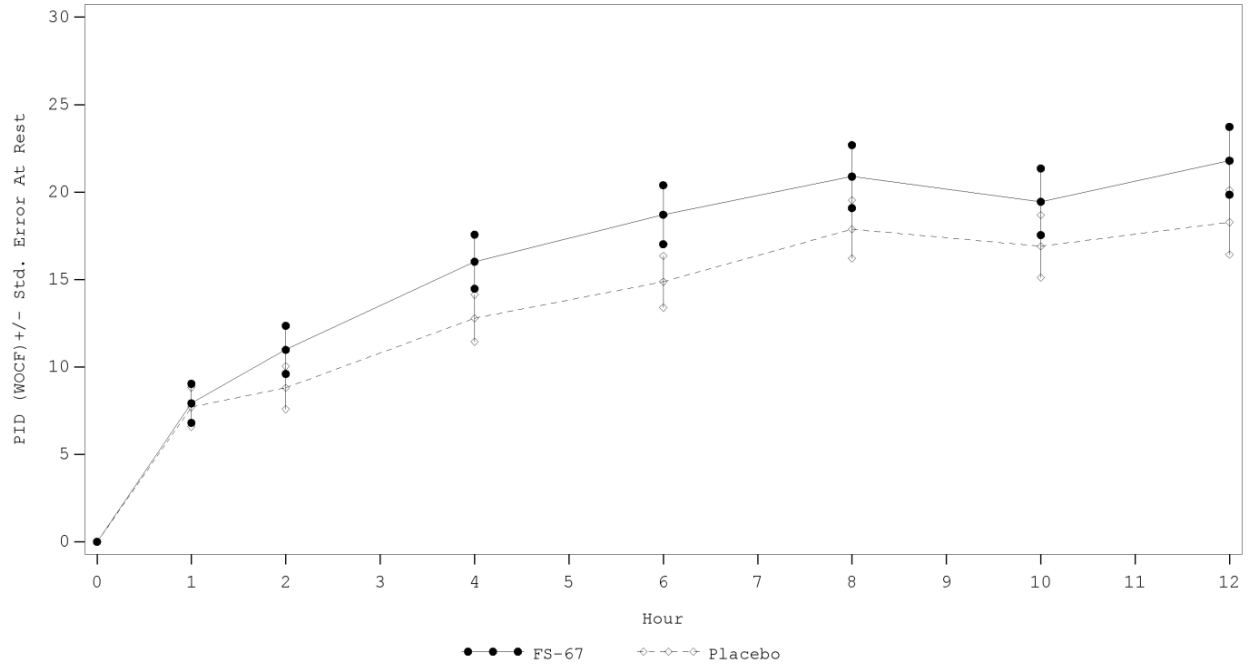
The magnitude of PID with respect to time was very similar between the two treatment groups during the first 12-hour and the entire 72-hour evaluation time period for pain at rest and pain upon weight bearing. The PID scores were approaching 20 mm up to Hour 10, around 30 mm by Hour 36, and about 50 mm up to Hour 72 for PI measured on 100 mm scale, suggesting contributing effects from spontaneous pain resolution and high placebo-patch response. The effect sizes of treatment differences were very small on the other hand, <4 mm (except Hour 20) for pain at rest and <3 mm for pain upon weight bearing during the 72-hour evaluation period (as shown in the table below). Clinically meaningful treatment differences in PID had not been demonstrated based on data collected and analyzed.

Table 7 Mean PID by VAS at Rest and upon Weight Bearing

	At rest			**Weight bearing**		
	FS-67	**Placebo**	**Difference**	**FS-67**	**Placebo**	**Difference**
Time	**N=126**	**N=126**		**N=126**	**N=126**	
1 Hour	7.921	7.706	0.215	6.437	6.437	0
2 Hours	10.984	8.810	2.174	10.675	9.778	0.897
4 Hours	16.024	12.786	3.238	14.873	12.389	2.484
6 Hours	18.706	14.873	3.833	17.500	14.746	2.754
8 Hours	20.889	17.873	3.016	19.155	18.310	0.845
Remedication	*14.372 (n=43)*	*14.771 (n=48)*	*-0.399*	*14.442 (n=43)*	*15.083 (n=48)*	*-0.641*
10 Hours	19.448	16.904	2.544	19.837	17.106	2.731
12 Hours	21.795	18.274	3.521	22.002	19.466	2.536
20 Hours	25.490	21.381	4.109	25.573	22.906	2.667
24 Hour	25.730	23.611	2.119	26.778	26.283	0.495
32 Hours	29.167	26.825	2.342	30.032	29.316	0.716
36 Hours	30.333	27.698	2.635	30.714	31.058	-0.344
44 Hours	32.897	29.717	3.18	34.381	33.120	1.261
48 Hours	33.595	30.921	2.674	35.587	34.518	1.069
56 Hours	35.952	33.254	2.698	38.929	36.927	2.002
60 Hours	37.357	34.516	2.841	41.341	38.468	2.873
68 Hours	40.254	37.302	2.952	44.071	41.175	2.896
72 Hours	48.651	45.310	3.341	52.968	51.214	1.754

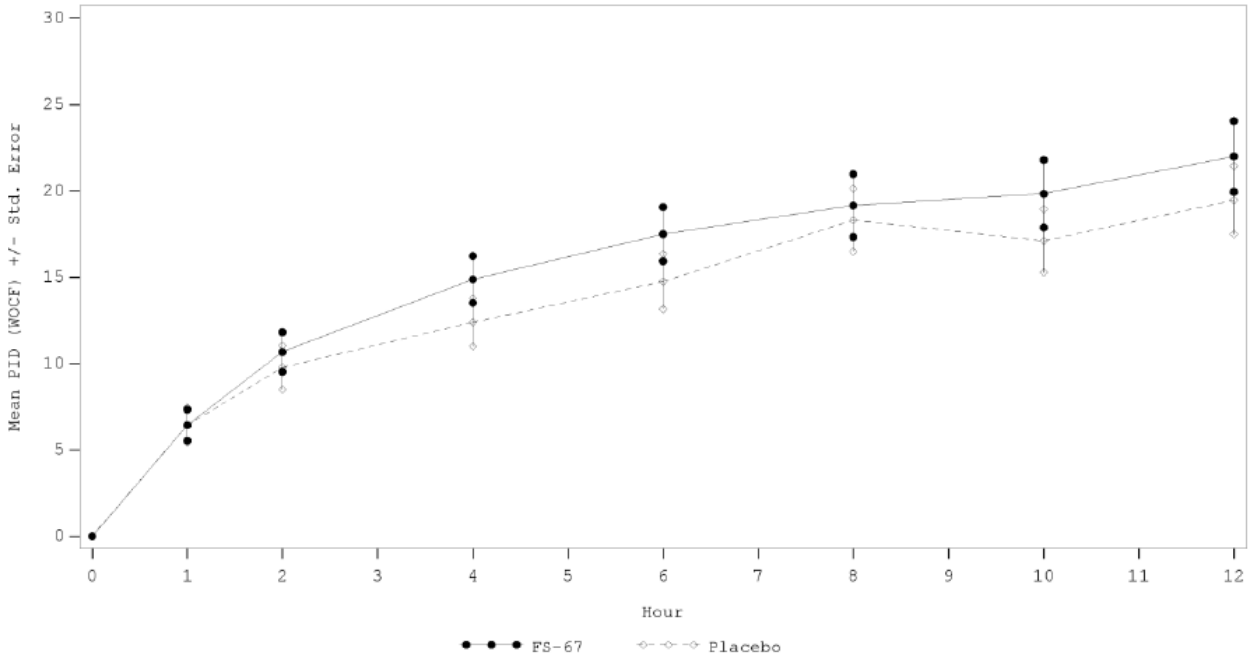
Source: Table 11-6 on page 64, Table 14.2.1.1.1 on pates 147-152, and Table 14.2.2.1 on pages 217-222 of the study report.

Figure 1 PID at Rest: Mean (± Standard Error), 0-12 Hours



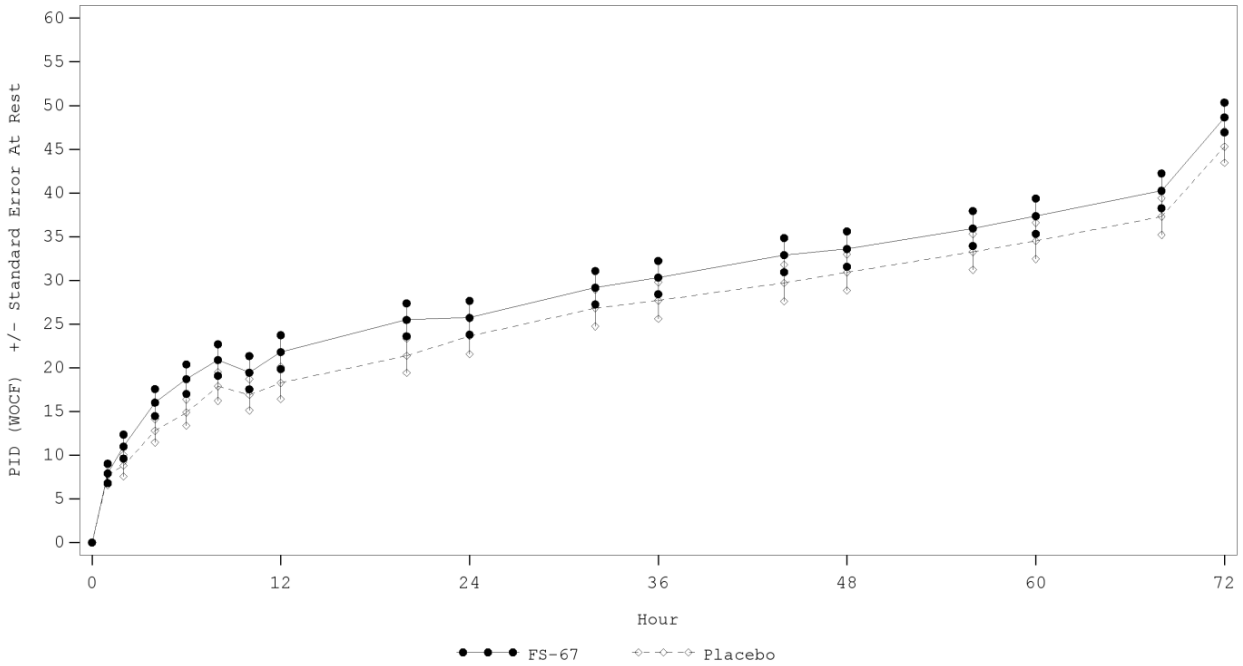
Source: Figure 11-2 on page 63 of the study report.

Figure 2 PID upon Weight Bearing: Mean (± Standard Error), 0-12 Hours



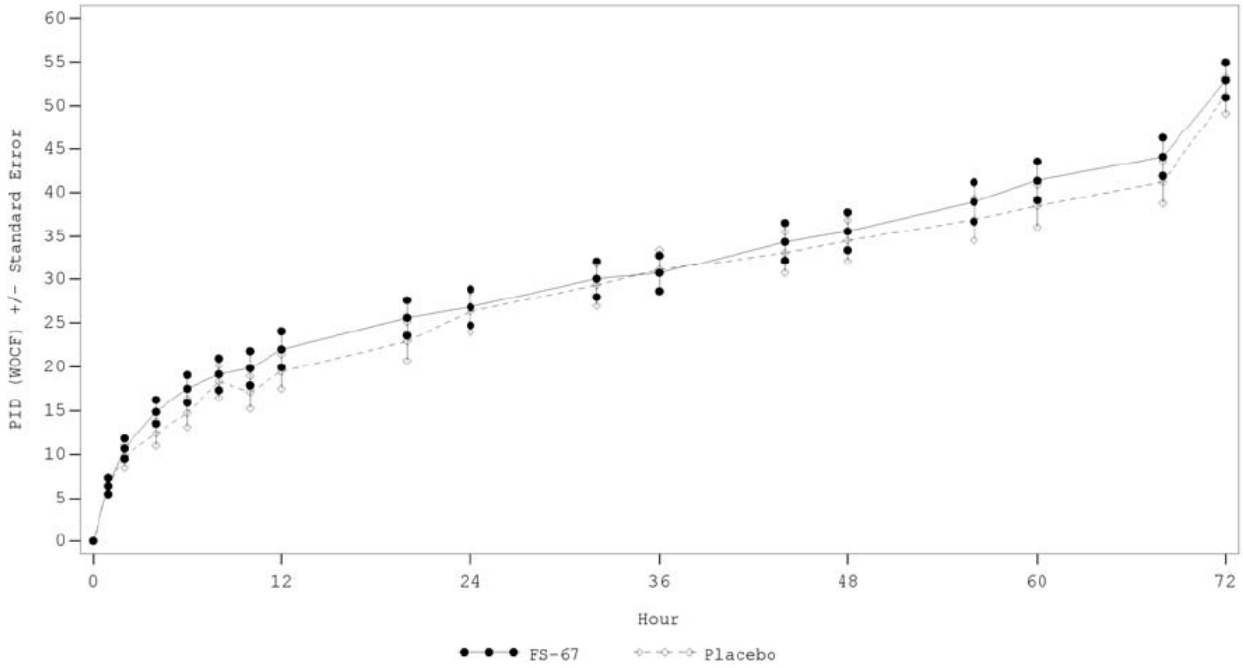
Source: Figure 11-3 on page 63 of the study report.

Figure 3 PID at Rest: Mean (± Standard Error), 0-72 Hours



Source: Figure 11-4 on page 66 of the study report.

Figure 4 PID upon Weight Bearing: Mean (± Standard Error), 0-72 Hours



Source: Figure 11-5 on page 66 of the study report.

Summed Pain Intensity Difference
Summed pain intensity difference or SPID at various time points are summarized in the table below.

Statistically significant treatment differences in SPID were shown for pain at rest and not for pain upon weight bearing. The treatment differences in SPID were from accumulation of very small and non significant differences in time-specific PID over time. Therefore, the differences are not considered clinically meaningful.

Table 8 SPID at Rest and upon Weight Bearing

	At rest				Weight bearing			
	FS-67 N=126	**Placebo N=126**	**Difference LSmean**	**P value**	**FS-67 N=126**	**Placebo N=126**	**Difference LSmean**	**P value**
SPID8	111.98	86.89	25.09	0.044	**107.19**	**89.13**	**18.06**	**0.137**
SPID12	191.79	150.48	41.32	0.039	190.64	158.27	32.38	0.106
SPID20	379.96	296.40	83.56	0.019	386.99	320.63	66.36	0.073
SPID32*	701.40	569.09	132.32		729.07	630.35	98.72	
SPID44	1071.33	887.58	183.76	0.031	1119.06	993.35	125.71	0.169
SPID56*	1480.55	1247.32	233.24		1563.38	1399.62	163.76	
SPID68	1930.17	1647.09	283.09	0.042	2066.53	1848.93	217.60	0.147
SPID72*	2104.86	1803.14	301.73		2259.37	2024.09	235.28	

* Exploratory efficacy endpoints
Source: Table 11-8 on page 67, Table 11-9 on page 68, Table 11-13 on page 71, Table 11-14 on page 72, Table 11-15 on page 73, Tables 14.2.5.1.1 and 14.2.5.1.2 on pages 254-257, Tables 14.2.5.2.1 and 14.2.5.2.2 on pages 259-262, and Tables 14.2.5.3.1 and 14.2.5.3.2 on pages 264-267 of the study report.

Time to Remedication (application of the second patch)
Data for time to remedication, or time to apply the second patch after the initial application, are summarized in the table and the Kaplan-Meier Curve below.

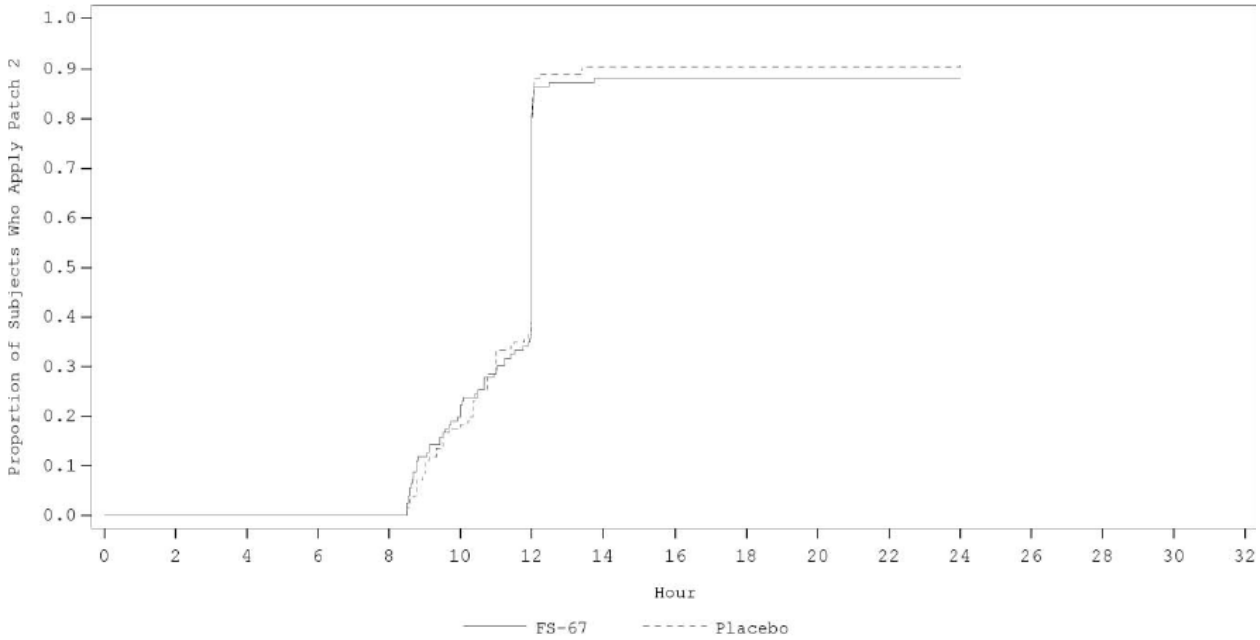
The mean and median time to remedication and the proportion using the second patch in the time interval between 8.5 and 12 hours (about 1/3 of both groups as estimated from the Kaplan-Meier Curve) were very similar between the two treatments.

Table 9 Time to Remedication

	Statistic	FS-67 N=126	Placebo N=126
Time to Remedication	n	111	115
	Mean	11.13	11.31
	(Standard Deviation)	(1.315)	(1.710)
	Median	12.00	12.00
	Minimum	8.5	8.5
	Maximum	13.8	24.0
Number of Events	n	126	126
	Remedication	111 (88.1%)	115 (91.3%)
	Censored [a]	15 (11.9%)	11 (8.7%)
Kaplan-Meier Estimates (95% Confidence interval)	25th Percentile	10.50 (9.6, 11.4)	10.50 (9.7, 11.0)
	Median	12.00 (12.0, 12.0)	12.00 (12.0, 12.0)
	75th Percentile	12.00 (12.0, 12.0)	12.00 (12.0, 12.0)
	P-value from Log-rank Test	0.641	

[a] Censored subjects are those subjects who did not apply a second patch with or without a negative response to the pain question. A remedication event is defined as any subject who applies a second patch with or without a positive response to the pain question.
Source: Table 11-17 on page 75 of the study report.

Figure 5 Time to Remedication within 32 Hours of the Initial Patch



Source: Figure 11-6 on page 75 of the study report.

Time to Rescue

Data on time to rescue during the entire 72-hour evaluation period are summarized in the table below. There were some noticeable treatment differences between the two groups, including 10% more subjects used rescue in the placebo group (23%) than the active treatment group (13%) and 8-hour earlier median time to rescue, 14 hours for the placebo group versus 22 hours for the active treatment group during the 72-hour evaluation period.

Table 10 Time to First Use of Rescue Medication

	Statistic	**FS-67 N=126**	**Placebo N=126**
Time to First Use of Rescue Medication	N	16	29
	Mean	19.73	22.34
	(Standard Deviation)	(9.208)	(17.176)
	Median	21.71	13.83
	Minimum	4.1	1.7
	Maximum	35.2	61.7
Number of Events	Used Rescue Medication, n (%)	16 (12.7)	29 (23.0)
	Censored [a], n (%)	110 (87.3)	97 (77.0
Kaplan-Meier Estimates (95% Confidence interval)	25th Percentile (95% CI)	NE(NE,NE)	NE (32.4, NE)
	Median (95% CI)	NE(NE,NE)	NE(NE,NE)
	75th Percentile (95% CI)	NE(NE,NE)	NE(NE,NE)
	P-value from Log-rank Test	0.032	

[a] Censored subjects are those who did not take any rescue medication defined as any rescue medication taken for the identified ankle injury after the date and time of the first patch application. Censored subjects are censored at their date of last contact
Source: Table 11-18 on page 77 of the study report.

Summary of findings

The randomized, double-blind, placebo-controlled, parallel, multiple-dose study of the combination patch applied every 12 hours for 3 days in adolescents with acute painful ankle sprain enrolled 252 patients, 126 in each treatment group. The two treatment groups were balanced with regard to the demographic and baseline characteristics and mean baseline pain intensity, which was 65 mm (on 100 mm VAS scale) for pain at rest and 75 mm for pain upon weight bearing. Two patients (both in the active treatment group) dropped out early: one was due to patch adherence problem and the other provided no explanation. About 40% in both treatment groups discontinued the patch before the end of 3-day treatment for no longer having pain associated with the identified injury.

The results did not show a statistically significant difference in the primary efficacy endpoint, SPID8 upon weight bearing. Treatment response in terms of time-specific PID was similar in both groups with the magnitude of PID of up to 20 mm by Hour 10, 30 mm by hour 36, and 50 mm by Hour 72. Treatment differences between the groups were very small with an effect size

of basically <4 mm for pain at rest and <3 mm for pain upon weight bearing during the entire 72-hour evaluation period.

There were no treatment differences in terms of the mean and median time to remedication after the initial patch and the proportion using the second patch. One third of both treatment groups applied the second patch in the time interval from 8.5 to 12 hours after the initial application. Rescue data from multiple patch applications revealed noticeable differences between the two groups in that 10% more subjects used rescue (23% on placebo versus 13% on active patch) and a median time to rescue of 8 hours earlier in the placebo group (14 hours) than the active treatment group (22 hours).

Efficacy conclusion

The results of the study have not demonstrated statistically significant treatment difference in the primary efficacy endpoint SPID8 or clinically meaningful separation of pain curves formed by time-specific PID, due to rapid pain resolution and high placebo response. Efficacy data do not support the use of Salonpas patch for treating external pain in adolescents aged 13 to 17 years.

Appendix

Eligibility Criteria

Inclusion criteria

1. Male or female, 13-17 years of age (inclusive)
2. Capable of understanding a parent's or study coordinator's explanation of the protocol
3. Capable of complying with the protocol
4. Willingness to give assent
5. Parental willingness to give permission and sign informed consent document
6. Capable of understanding and providing pain evaluations
7. Able to stay at study site during applicable evaluation periods
8. Clinical diagnosis of painful acute benign unilateral side ankle sprain of the lateral ligament(s) based on provided clinical criteria; ankle sprain must be Grade 1 (partial tear of ligament) or Grade 2 (incomplete tear of ligament, with moderate functional impairment)
9. Ankle sprain injury occurred within 72 hours of the day on which baseline assessments and application of Patch 1 occur (Day 1)
10. VAS pain intensity score (current) 50 mm to 85 mm (inclusive) at rest, and VAS pain intensity score upon monopodal weight bearing that is higher than the corresponding score at rest, both at screening and at baseline (on Day 1 before application of Patch 1)
11. Females must be consistently (≥ 3 months) sexually inactive/abstinent, or if sexually active must be using 2 methods of contraception, one of which must be a barrier method. Allowable contraceptive methods must have a failure rate < 1% and may include the following (if used consistently for ≥ 3 months): condoms; diaphragm in combination with a spermicide; intrauterine device (IUD); oral contraceptives; or contraception implants or patches. The subject must agree to continue abstinence or identified contraceptive methods throughout the study and for ≥ 1 week after the final study patch is removed.

Exclusion criteria

1. Any signs or symptoms potentially related to chicken pox or influenza or exposure to someone with chicken pox within the previous 3 weeks or influenza within the previous 1 week
2. Receipt of varicella and/or influenza immunizations in the 2 weeks preceding study entry
3. Grade 3 ankle sprain (complete tear of ligament, severe pain, swelling, tenderness, inability to weight bear or ambulate)
4. Inability to perform required weight-bearing assessments (monopodal for 1 second)
5. Clinical evidence that the area of ankle sprain is associated with chronic pain, multiple injuries, or bone fracture within the past 6 months
6. Lack of any visible signs of ankle sprain (e.g., complete absence of swelling or other signs indicating a true ankle sprain) upon initial presentation
7. Symptoms attributable to primary inflammatory diseases of the joint (e.g., Achilles tendonitis, Achilles peritendonitis, achillobursitis, medial tibial stress syndrome, metatarsal stress fracture, plantar fasciitis, exostosis, impingement exostoses, retrocalcaneal bursitis, osteochondritis dissecans, peroneal tendon subluxation, and/or peroneal nerve entrapment)
8. Symptoms attributable to any dermatitis near the area of patch application
9. Contraindications in opinion of the Investigator that preclude use of methyl salicylate or menthol
10. Significant renal impairment
11. Uncontrolled heart failure
12. Uncontrolled hypertension, stroke, or transient ischemic attack within 6 months
13. Significant active hepatic disease

14. History of neoplastic disease
15. History of hypersensitivity, contraindication, or allergy to salicylates, menthol, or acetaminophen
16. History of hypersensitivity or allergy to topical preparations, adhesive dressings, or natural rubber
17. History of aspirin-induced asthma
18. Current infectious disease with or without fever
19. Need for warfarin or other anticoagulant medicine
20. History of coagulopathy (e.g., hemophilia, platelet disorder)
21. Pregnancy or lactation
22. Presence at treatment site of any skin abnormality likely to be aggravated by study patches such as infection, rash, atrophy, excessive fragility or dryness, cuts, or abrasions (swelling and/or ecchymosis allowable)
23. Expected surgery during study participation
24. Psychiatric condition or history of substance abuse that, in opinion of Investigator, may interfere with study participation
25. History of peptic ulcer disease or inflammatory bowel disease
26. History of any AEs relating to any formulation of any non-steroidal anti-inflammatory drug (NSAID)
27. Administration (from the time of ankle injury) to the affected area of CO2 laser therapy, transcutaneous electrical nerve stimulation (TENS), ultrasound, or iontophoresis
28. Receipt or use within 2 hours before baseline pain assessments of any of the following: thermal therapy, cryotherapy, topically-applied ice, massage, stretching, compression, clasps, bands, splints, casts, or other supports (note: use of crutches is not encouraged but is permitted if necessary; however, pain assessments must be performed without crutches)
29. Currently receiving active physical therapy for the ankle sprain or scheduled to undergo such treatment during study period
30. Use of topical counterirritants (e.g., methyl salicylate or capsaicin) since the subject had the ankle sprain, or anticipated need for topical medicine (other than study drug) or dressing during the study to any area of the body
31. Use of another investigational drug or device or participation in any other clinical study within 1 month before study entry
32. Use of any analgesic medication or other medication that could confound assessment of analgesic response (see Appendix C)
33. Use of any NSAID within protocol-defined time period before application of Patch 1 (e.g., 12 hours for ibuprofen; see Appendix C for other NSAIDs)
34. Use of acetaminophen within 12 hours before application of Patch 1
35. Taking a prohibited medication or other treatment within protocol-defined timeframes (see Appendix C)
36. Any pending litigation pertaining to the cause of the subject's pain
37. Considered by Investigator to be unsuitable for objectives of study

6 Review of Efficacy

Efficacy Summary

In this randomized, double-blind, placebo-controlled, multiple-dose study of FS-67 patch 252 adolescents (126 per study group) aged 13 to 17 years with painful acute ankle sprain were treated with the study patch applied to the affected area for 8 hours with a dosing frequency of every 12 hours for up to 6 applications. The results revealed balanced demographic characteristics and baseline pain intensity (65 mm for pain at rest and 75 mm for pain upon weight bearing on a 100 mm scale) between the treatment groups, very low rate of dropouts (n=2), relatively low rate of protocol deviation (12%), mostly due to deviation from inclusion criteria in terms of baseline pain intensity in both groups.

A statistically significant difference was not shown in the primary efficacy endpoint, SPID8 upon weight bearing. The treatment differences between the FS-67 and placebo patch in all the time-specific PID and SPID summed over various time intervals at rest and upon weight bearing are very small. The possible explanations are rapid pain resolution and high placebo response as suggested by 40% pain resolution during the 3-day treatment period and high response rate of PID reaching 50 mm by Hour 72 in both treatment groups. The mean and median time to remedication and the proportion using the second patch were also very similar between the two groups. The only noticeable treatment differences were 10% more subjects used rescue in the placebo group and 8-hour earlier median time to rescue during the multiple-patch treatment.

In summary, efficacy data from this study do not support the use of Salonpas patch in adolescents aged 13 to 17 years.

6.1 Indication

Temporarily relieves mild to moderate aches and pains of muscles and joints associated with strains, sprains, simple backache, arthritis, and bruises

6.1.1 Methods

The NDA contains one adequately designed and well-controlled efficacy study in adolescents. The details about study design, major components of the protocol, study conduct, and efficacy results are presented in Section 5.3 of this review.

6.1.2 Demographics

The study population consisted of 252 adolescents aged 13 to 17 years with a mean age of 15 years, 75% Caucasian, 16% African American, and 40% female. The treatment groups were approximately balanced with regard to demographic characteristics and baseline pain intensity

(PI), which was about 65 mm (on 100 mm VAS scale) for pain at rest and 75 mm for pain upon weight bearing.

6.1.3 Subject Disposition

Of the 252 patients treated with study patches, only two (both in the FS-67 group) had early terminations with explanations for dropping out as problems with patch adherence in one and unknown in the other. About 40% of the study population, 50 patients in the FS-67 group and 52 patients in the placebo group, discontinued the use of patches early due to pain resolution and were not considered as dropouts.

6.1.4 Analysis of Primary Endpoint(s)

All 252 treated patients were included in the mITT population for primary analysis. The LS mean difference in SPID8 (VAS) upon weight bearing between the FS-67 and placebo patch groups was very small and not statistically significant (107.2 for FS-67 treatment versus 89.1 for placebo treatment).

6.1.5 Analysis of Secondary Endpoints(s)

All the time-specific PID and SPID endpoints designated as secondary and exploratory efficacy endpoints are grouped together under PID and SPID for ease of presentation.

Time-specific PID

The magnitude of PID with respect to time were similar in both treatment groups, approaching 20 mm up to Hour 10, around 30 mm by Hour 36, and about 50 mm up to Hour 72 for PI measured on an 100 mm scale, suggesting contribution from rapid spontaneous pain resolution and high response to placebo patch. The effect sizes of treatment differences were relatively very small, <4 mm (except Hour 20) for pain at rest and <3 mm for pain upon weight bearing, and are not considered clinically meaningful.

Summed Pain Intensity Difference, SPID

Statistically significant treatment differences in SPID were shown for pain at rest and not for pain upon weight bearing. The statistically significant small treatment differences in SPID at rest in this case resulted from accumulation of very small and non significant differences in time-specific PID over time and, therefore, are not considered clinically meaningful.

Time to Remedication (application of the second patch)

The mean and median time to remedication (about 11 hours for mean and 12 hours for median) and the proportion using the second patch (about 1/3 in both groups) in the time interval between 8.5 to 12 hours after the initial patch application were very similar between the two treatments.

Time to Rescue

There were some noticeable treatment differences in terms of time to rescue between the two groups, including 10% more subjects used rescue in the placebo group (23% versus 13%) and 8-hour earlier median time to rescue (14 hours versus 22 hours) as compared to the active treatment group during the 72-hour multiple-patch evaluation period.

6.1.6 Other Endpoints

PID and SPID classified as exploratory efficacy endpoints are summarized together with those classified as secondary efficacy endpoints above.

6.1.7 Subpopulations

Subpopulation efficacy analyses were not conducted.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The findings of the efficacy study in adolescents did not suggest changes in dosing recommendations in the approved Salonpas® labeling.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Efficacy has not been demonstrated by the results of the study.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Refer to the NDA review by Dr. Ryan Raffaelli.

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

7.1.2 Categorization of Adverse Events

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.2 Explorations for Dose Response

7.2.3 Special Animal and/or In Vitro Testing

7.2.4 Routine Clinical Testing

7.2.5 Metabolic, Clearance, and Interaction Workup

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

7.3 Major Safety Results

7.3.1 Deaths

7.3.2 Nonfatal Serious Adverse Events

7.3.3 Dropouts and/or Discontinuations

7.3.4 Significant Adverse Events

7.3.5 Submission Specific Primary Safety Concerns

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

7.4.2 Laboratory Findings

7.4.3 Vital Signs

7.4.4 Electrocardiograms (ECGs)

7.4.5 Special Safety Studies/Clinical Trials

7.4.6 Immunogenicity

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

7.5.2 Time Dependency for Adverse Events

7.5.3 Drug-Demographic Interactions

7.5.4 Drug-Disease Interactions

7.5.5 Drug-Drug Interactions

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

7.6.2 Human Reproduction and Pregnancy Data

7.6.3 Pediatrics and Assessment of Effects on Growth

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

Refer to the NDA review by Dr. Ryan Raffaelli.

9 Appendices

Refer to the NDA review by Dr. Ryan Raffaelli.

9.1 Literature Review/References

9.2 Labeling Recommendations

9.3 Advisory Committee Meeting

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

/s/

CHRISTINA L FANG
02/25/2013

SHARON H HERTZ
02/25/2013
I concur.