



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/BLA #:** 22-029  
**Supplement #:** 012  
**Drug Name:** SALONPAS pain relief patch  
**Indication(s):** Temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises and sprains  
**Applicant:** Hisamitsu Pharmaceutical Co., Inc.  
**Date(s):** Letter date: May 31, 2012  
PDUFA date: March, 29, 2013  
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## **1. EXECUTIVE SUMMARY**

Hisamitsu has submitted a supplemental New Drug Application for SALONPAS pain relief patch seeking an indication 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 aged 13 to 17 years. I conclude that the study failed to provide evidence of efficacy of SALONPAS pain relief patch in comparison to placebo patch.

The submission contained one efficacy study. Study FS-67-HP01-E02 was a randomized, double-blind, placebo-controlled, parallel group, multicenter study in adolescent patients with grade 1 or 2 ankle sprain. Eligible patients were randomized to receive either SALONPAS or placebo patches in a 3-day treatment period.

The primary efficacy endpoint was the summed pain intensity difference at 8 hours after dosing (SPID8) for weight bearing response. Secondary endpoints were SPID8 at rest, SPID12, SPID20, SPID44 and SPID68 upon monopodal weight bearing and at rest, time to application of remediation and time to administration of rescue medication.

The primary analysis was an analysis of covariance (ANCOVA) with baseline pain as a covariate and treatment and pooled center as factors. The primary imputation was last observation carried forward (LOCF) for patients discontinuing study patches due to pain resolution and worst observation carried forward (WOCF) for patients discontinuing study patches due to other reasons. In July 2010, the National Academy of Sciences (NAS) released a report on the prevention and treatment of missing data. The NAS report discourages single imputation methods. However as there were no patients discontinuing study patches during the first 8 hours when the primary outcome was assessed, missing data was not an issue.

Based on my review, I conclude that SALONPAS pain relief patch failed to reduce the pain intensity in adolescent patients 13 to 17 years of age with grade 1 or 2 ankle sprain when compared to placebo.

## **2. INTRODUCTION**

### **2.1 Overview**

SALONPAS pain relief patch was approved on February 20, 2008 for over-the-counter use in adults to temporarily relieve mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises and sprains. The pediatric study required under the Pediatric Research Equity Act was deferred at the time of approval of SALONPAS pain relief patch. On March 20, 2008, the agency agreed with Hisamitsu's plan to first study children aged 13 to 17 years and then to address the advisability of clinical evaluations in younger children. Hisamitsu has completed two required pharmacokinetic studies and one clinical safety and efficacy study in children from 13 to 17 years old. Following several communications between the applicant and the agency, Hisamitsu submitted the efficacy supplement in May 2012.

The submission contained one efficacy study. Study FS-67-HP01-E02 was a multicenter, randomized, double-blind, placebo-controlled, parallel group study in adolescent patients 13 to 17 years of age with grade 1 or 2 ankle sprain.

**Table 1: List of the study included in this review**

Study Number (Dates Conducted)	Number of Centers (Locations)	Sample Size	Type of Control	Design	Duration of Treatment
FS-67-HP01-E02  (12/2009 – 10/2010)	US: 24 sites	Randomization: FS-67 Patch* n=126  Placebo n=126	placebo	randomized, double-blind, placebo-controlled, parallel group, multicenter study in adolescents	up to 6 patches applied over 3 days

**Source:** Reviewer’s analysis

\*: FS-67 Patch is the SALONPAS patch

## 2.2 Data Sources

The initially submitted datasets didn’t include all patients enrolled in the study. On July 17, 2012, we requested the applicant submit raw and analysis-ready datasets for all patients. The applicant submitted additional datasets per the Division’s request. All data was supplied electronically as SAS transport files and can be found at the following location in the CDER electronic document room: <\\CDSESUB4\NONECTD\NDA022029\5116645>.

## 3. STATISTICAL EVALUATION

### 3.1 Data and Analysis Quality

The electronic data submitted was of sufficient quality to allow a thorough review. I was able to reproduce the primary outcome as well as the secondary variables of interest.

### 3.2 Evaluation of Efficacy

#### Study Design and Endpoints

The primary objective of Study FS-67-HP01-E02 was to evaluate the efficacy and safety of single and multiple applications of SALONPAS patches in adolescent patients with ankle sprain.

After screening, eligible patients were randomized in a 1:1 ratio to receive either active SALONPAS (referred to as FS-67 during development) or placebo patches. Patients serially applied up to 6 study patches over a 3-day treatment period. Each study patch was applied for 8 hours and then removed. Subsequent patch applications were to occur at 12-hour intervals with the possible exception of the second patch which could be applied earlier (remedication). Before each subsequent scheduled patch application, patients were required to provide a response to an inquiry regarding pain upon monopodal weight bearing. Only those patients who indicated ankle sprain pain upon monopodal weight bearing were to apply the next scheduled study patch.

Patients who did not indicate pain upon monopodal weight bearing on the affected ankle were to discontinue the patch applications and were followed for use of rescue and concomitant medications and safety assessments.

The primary efficacy endpoint was the SPID8 upon monopodal weight bearing. Pain was measured on a 100 mm visual analog scale (VAS) whereby 0 mm represented no pain and 100 mm represented the worst pain imaginable. On Day 1, VAS assessments were completed and observed by the staff in the clinic at 1, 2, 4, 6, 8 hours ( $\pm$  10 minutes) after application of patch 1. Patients continued to complete subsequent VAS assessments at home, including 10 and 12 hours after patch 1 application. Subsequent VAS assessments were performed within 15 minutes before each scheduled patch application time and within 15 minutes before removal of each patch. A final VAS score was obtained on Day 4.

### **Patient Disposition, Demographic and Baseline Characteristics**

The demographics for all randomized patients are presented in the appendix. The majority of the patients were white (73%), and approximately 59% of all patients were male. The mean age was 15 years.

The disposition of patients is shown in Table 2. Completers were defined as patients who returned for the Day 4 assessment and had not withdrawn from the study. This could include patients discontinuing study treatment early. Almost all randomized patients completed the study with the exception of 2 patients discontinuing from the study due to reasons classified as “other”. The disposition of patients who discontinued study treatment early is shown in Table 3. Due to pain resolution, 40% of patients in the active treatment group and 41% of patients in the control group discontinued patches early. An information request (IR) dated July 17, 2012 was sent to gain information on when these patients discontinued the study patch. The applicant responded and provided a complete dataset which included a date and time of last patch removal for each patient. There were no patients that discontinued study treatment during the first 8 hours after patch application.

**Table 2: Patients’ disposition**

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Numbe

Numbe

Numbe

Numbe

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this

**Source:** Clinical Study Report Table 10-1

**Table 3: Patients who discontinued study treatment early**

Subject

Yes <sup>a</sup>

No

<sup>a</sup> Ye

**Source:** Clinical Study Report Table 10-3

### Statistical Methodologies

For the primary efficacy variable, the treatment groups were compared using an ANCOVA model with factors for treatment, pooled study site and baseline pain intensity as a covariate. The primary analysis population was the modified intention-to-treat (mITT) population which included all randomized patients who received at least one patch and had a baseline and at least one post-baseline VAS upon monopodal weight-bearing assessment.

The primary method of handling missing data was LOCF for patients discontinuing study patches due to no pain associated with the identified ankle injury and WOCF for patients discontinuing study patches due to other reasons. A sensitivity analysis used a LOCF approach for all discontinuations.

For rescue medication, the applicant stated that “If a subject took rescue medication during the treatment phase of the study then all values recorded on or after the start date of rescue medication were replaced with the appropriate value recorded before start date of the rescue medication.” An IR dated July 17, 2012 was sent to gain clarification for the definition of the “appropriate” value. The applicant responded that the “appropriate value” used in the primary analysis was the worst pain value recorded between the baseline and the use of the first rescue medication. In the sensitivity analysis, the “appropriate value” was the last pain value recorded prior to the use of the first rescue medication.

### Results and Conclusions

Subjects were enrolled from 24 sites in the United States. Two hundred and fifty-two subjects were randomized in the study. The mITT analysis set included all 252 randomized subjects.

Table 5 shows the applicant’s primary efficacy analysis. I was able to replicate the applicant’s findings. Adolescent patients receiving SALONPAS pain relief patches didn’t have a greater reduction in pain intensity compared to adolescent patients receiving placebo patches.

**Table 4: Primary efficacy results**

	<b>FS-67 (n=126)</b>	<b>Placebo (n=126)</b>	<b>LS treatment difference</b>
<b>Least-Square Means (SE)</b>	107 (9)	89 (9)	18 (12)
<b>95% CI</b>	(89, 125)	(71, 108)	(-6, 42)
<b>P-value</b>			0.137

**Source:** Clinical Study Report Table 11-9 and Reviewer’s Analyses

### **3.3 Evaluation of Safety**

The evaluation of the safety data was conducted by Dr. Christina Fang. No additional review of the safety data was requested, and the reader is referred to Dr. Fang's review for detailed information regarding the adverse event profile. The risks appear consistent for this drug type.

## **4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

As the primary efficacy analysis failed to demonstrate the efficacy of SALONPAS pain relief patch, neither the applicant nor I conducted subgroup analyses.

## **5. SUMMARY AND CONCLUSIONS**

### **5.1 Statistical Issues**

Single imputation methods are discouraged by the NAS report released in July 2010. However since there was a high study completion rate and there were no patients discontinuing study patches at hour 8 after the application, missing data was not an issue for the primary efficacy analysis. There were no other statistical issues identified.

### **5.2 Collective Evidence**

The efficacy study submitted in the current supplement failed to provide adequate evidence of the analgesic effect of SALONPAS pain relief patch in patients aged 13 to 17 years.

### **5.3 Conclusions and Recommendations**

Based on my review, I conclude that SALONPAS pain relief patch does not reduce pain intensity in adolescent patients.

### **5.4 Labeling Recommendations**

The submitted pediatric study was not statistically significant. Hence, the applicant planned to employ the same labeling as approved previously, with the exception of new information relating to the pediatric population under Directions:

*Children under 18 years of age: do not use.* [REDACTED] (b) (4).

Comment: The review team will need to make a decision whether the added information is appropriately worded. I question whether the use of [REDACTED] (b) (4) is appropriate as a study was conducted, but it failed to demonstrate the efficacy of SALONPAS pain relief patch in adolescent patients.



**APPENDIX: Summary of Demographics and Baseline Characteristics**

**Study FS-67-HP01-E02 (source: Clinical Study Report Table 11-2)**

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**Study FS-67-HP01-E02 (source: Clinical Study Report Table 11-3)**

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**Signature/Distribution List**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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02/21/2013

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