CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-029

STATISTICAL REVIEW(S)

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

COMPLETE RESPONSE/CLINICAL STUDIES

NDA:	22-029
Drug Name:	SALONPAS ——— b(4)
	(10% methyl salicylate & 3% L-menthol)
Indication(s):	Temporarily relieves mild to moderate aches & pains of muscles & joints associated with arthritis, simple backache, strains and sprains
Applicant:	Hisamitsu Pharmaceutical Co., Inc.
Date(s):	Submitted: August 20, 2007
	PDUFA Due Date: February 20, 2008
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Yongman Kim, Ph.D.
Concurring Reviewers:	Dionne Price, Ph.D.
Medical Division:	Division of Anesthesia, Analgesia, and Rheumatology Products
Clinical Team:	Christina Fang, M.D.
Project Manager:	Keith Olin

Keywords: Complete response, reanalysis

1 Background

Hisamitsu originally submitted NDA 22-029 on February 27, 2006. The applicant proposed the use of SALONPAS for the temporary relief of mild to moderate aches & joints associated with arthritis, simple backache, strains, bruises and sprains. In my review of the NDA, I concluded that the pivotal study FS-67-E02 provided substantial evidence of efficacy of SALOPAS. My conclusion was based on the statistically significant difference between the SALONPAS and placebo groups in terms of summed pain intensity differences over 8 hours.

Upon completion of the review, the Agency issued an Approvable Letter.
In the action letter dated December 27, 2006, the Agency requested that Hisamitsu conduct an additional clinical study to define the duration of effect. The following excerpt is from the action letter:

> Your single-patch study was not adequate to establish the dosing interval for your product, and thus cannot be labeled for consumer use. The data do not support use of a second dosing period [redacted] over 25 hours. Therefore to address these concerns you must perform an adequate and well-controlled study to define the duration of effect and to demonstrate efficacy and safety over the proposed duration of use for which the patch will be labeled. b(4)

In a post-action meeting on February 8, 2007, the Agency and the applicant discussed the applicant's planned responses to the comments in the AE letter.

In the complete response submitted on August 20, 2007, the applicant conducted a re-analysis on the data from the pivotal study FS-67-E02 in the original NDA. The applicant did not conduct a new study. The following excerpt is from the complete response:

> As will be fully discussed in this response, the data generated in the pivotal NDA trial (FS-67-E02) has been independently reanalyzed to address FDA's concerns relating to the duration of patch efficacy and establishment of proper dosing intervals. Subsequent to our February 8, 2007 meeting with FDA. Hisamitsu retained an independent statistical consultant, [redacted] to evaluate FS-67-E02 and FDA's review of these study data. b(4)
>
> This reanalysis amplifies the previously provided analyses and clearly establish that the SALONPAS [redacted] provided effective pain relief throughout its 8 hour application period. However, [redacted] finds no treatment-related pain relief is evidenced following patch removal (during the 9-12 hours post application observation period). These data clearly establish the 8 hour duration of efficacy. As such, pursuant to FDA's correspondence dated October 29, 2004, a multiple-dose efficacy study is not required because both the onset (up to b(4)

3 hours) and duration (8 hours) of pain relief have been established with the pivotal single dose clinical trial.

The re-analyses are the subject of the current review. The review has been formulated based on the submissions and discussions arising from interactions outlined in Table 1.

Table1. Timeline of Post-Action Interactions

Date	Correspondence
27 February 2006	NDA 22-029 submitted by Hisamitsu, Inc.
27 December 2006	Approvable letter issued.
8 February 2007	Post action meeting requested by Hisamitsu to receive clarification from the division on clinical and statistical issues.
20 August 2007	Complete Response was submitted.

2 Review

2.1 Study Design

Study FS-67-E02 was a 12-hour, multi-center, double-blind study of the safety and efficacy of FS-67 topical patch compared to placebo patch in subjects with muscle strain. Two-hundred and eight eligible patients were randomized to FS-67 or placebo in 1:1 ratio at 15 sites.

The applicant defined the primary efficacy endpoint as the summed pain intensity difference at 8 hours (SPID8) with movement. SPID8 was a time-weighted sum of pain and was calculated using the following formula:

$$SPID8 = \frac{1}{2} PID0.5 + \frac{1}{2} PID1 + PID2 + \ldots + PID8$$

where PIDi denoted the pain intensity difference at hour i. The pain intensity difference (PID) was calculated using the following formula:

PIDi =pain intensity at baseline – pain intensity at hour i

Pain intensity was measured using a visual analog scale (VAS) that ranged from 0 ("no pain") to 100 ("extreme pain") in mm.

2.2 Statistical Methodologies

In the original NDA, the primary efficacy outcome was compared between SALONPAS topical patch and placebo using an analysis of variance (ANOVA) model with terms for treatment and center. Two centers, center 04 and center 13, were pooled because of too few subjects.

In the current submission, the applicant conducted new analyses to demonstrate that there was no statistically significant difference between the topical patch and placebo after removing the patch. The applicant used a repeated measure mixed model on SPID10, SPID11 and SPID12. The applicant provided the following rationale for the methodology:

Bckground of the Pivotal Phase III Study

This clinical trial was conducted by the [redacted] and their statisticians conducted the statistical analyses submitted with the Hisamitsu NDA. Using their procedures, [redacted] reported that significant treatment group differences were calculated for both the SPID8 and for the SPID12 calculations. However, as summarized below, it appears that their calculations did not address the longitudinal nature of the reported data and did not ensure that

b(4)

treatment group randomization was maintained throughout the study. As such, their analyses incorrectly extend the duration of the actual pain relief afforded by the active patch formulation (from 8 hours to 12 hours).

b(4)

The Analyses Conducted by

As noted in his report, ——— reviewed Hisamitsu's Special Clinical Protocol Assessment, the FDA-approved Statistical Analysis Plan (IND #62,735 A039), the — study report and statistical analyses relating to FS-67-E02 and FDA's evaluation of these reports. Following this, ——— performed a reanalysis of the efficacy data. As fully described in Attachment #1, Dr. ——— did not rely upon the assumptions and analyses adopted by ——— when evaluating the efficacy data generated in the pivotal Phase III study. ———employed the original pre-study baseline randomization data for all treatment group comparisons even those generated following removal of the patches. Rather, ——— employed several statistical models to explore the relationship between treatment and outcome for the period spanning 9-12 hours following patch application (also corresponding to 1 to 4 hours following patch removal). Because randomization at the start of the study did not guarantee 9 hour treatment group comparability, adjustments for imbalances in the 9 hour SPID were found to be required.

Repeated measure models were then generated to compare the active and placebo patches between 10 and 12 hours using the 9 hour data as a covariate. Notwithstanding the models employed, there were no significant treatment group differences for either the Intent-To-Treat or Per-Protocol populations. Given these results, the duration of the SALOPAS ——— has been established at 8 hours and there is no statistically derived evidence for a lingering depot effect. ———

b(4)

2.3 Results

The following tables present results for Study FS-67-E02 submitted from the original NDA submission and analyses from the current submission. An ANOVA model with terms for treatment and center was used the in original analysis. A repeated measures mixed model with terms for treatment, center, visit, subject and the 9 hour SPID as covariate was used in the reanalysis.

Results from the original NDA submission:

As shown in Table 2, the statistically significant difference between SALONPAS and placebo was shown in the analysis using a LOCF imputation strategy.

Table 2. Applicant's Primary Analysis (SPID8 with Movement): ITT LOCF

SPID8 WITH MOVEMENT		
	FS-67 (N=105)	**PLACEBO (N=103)**
LSMean (SE)	189.6 (13.2)	137.5 (13.3)
Diff. from PBO (95% CI)	52.1 (16.2, 88.0)	
p-value	.0047	

LSMeans and p-values calculated from ANOVA model: Y = trt + center.

Results from the current submission:

Tables 3-4 present results from the current submission. Analyses did not show a statistically significant difference between SLONPAS and placebo.

Table 3. Applicant's Reanalysis of SPIDi with Movement after Hour 8: ITT

Difference	SE	p-value
-0.8825	0.9018	0.3290

Repeated measures mixed model on SPID10, SPID11, SPID12. Model includes terms for treatment, center, visit, and SPID9 as covariate. Analysis results from Appendix 1 in Page 47 of Vol. 1.

Table 4. Applicant's Reanalysis of (SPIDi-SPID9) with Movement after Hour 8: ITT

Difference	SE	p-value
-0.4827	0.9123	0.5974

Repeated measures mixed model on SPID10-SPID9, SPID11-SPID9, SPID12-SPID9. Model includes terms for treatment, center, visit, and SPID9 as covariate. Analysis results from Appendix 1 in Page 47 of Vol. 1.

3 Conclusions and Recommendations

The applicant has conducted re-analyses to demonstrate that there is no statistically significant difference between treatment groups in summed pain intensity with movement after removal of topical patches. b(4)

In general, dosing intervals are often established using PK data and multiple-dose safety and efficacy data. However, given the intended use of this product and the safety of the product, the clinical team finds sufficient evidence (in the absence of multiple-dose efficacy data) to support the proposed dosing regime proposed by the applicant. The clinical rationale is provided in Dr. Christina Fang's review.

Based on my evaluation, the data from the original submission demonstrates the effectiveness of the product as measured by the summed pain intensity difference over 8 hours.

The re-analyses were exploratory and post-hoc in nature. Several concerns arose during my assessment of the re-analyses including the validity of the assumption regarding imbalance after 8 hours and the arbitrary evaluation of ineffectiveness after 8 hours. However since the clinical team did not consider any re-analyses of single-dose efficacy data to be useful in determining the approvability of the drug, I did not further investigate my concerns.

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/s/

Yongman Kim
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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/Serial Number:	NDA 22-029
Drug Name:	Salonpa[redacted] b(4)
Indication(s):	Temporarily relieves mild to moderate aches & joints associated with arthritis, simple backache, strains, bruises and sprains
Applicant:	Hisamitsu Pharmaceutical Company, Inc.
Date(s):	Submitted: February 27, 2006 PDUFA: December 27, 2006
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Yongman Kim, Ph.D.
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Medical Division:	Division of Anesthesia, Analgesia, and Rheumatology Products
Clinical Team:	Christina Fang, M.D. Joseph Porres, M.D.
Project Manager:	Keith Olin

Keywords: NDA review, clinical studies, sum of pain intensity difference with movement

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Study FS-67-E02 was conducted in subjects with muscle strain and showed a statistically significant difference between FS-67 topical patch and placebo patch in the summed pain intensity difference (SPID) with movement from baseline to hour 8. The study additionally demonstrated significant differences in several secondary efficacy outcomes including the SPID8 at rest, total pain relief with movement and at rest at hour 8 (TOTPAR8), and the pain intensity difference (PID) with movement over 1 to 8 hours between FS-67 topical patch and placebo patch. There were no significant differences in the time to onset of perceptible pain relief or the time to onset of meaningful pain relief.

Overall, the study was successful in showing superiority of FS-67 topical patch over placebo in terms of pain reduction in the acute setting. However, the study failed to provide evidence of superiority of FS-67 in terms of the time to onset of analgesia, a measure of interest to the clinical review team.

1.2 Brief Overview of Clinical Studies

The sponsor submitted the results and data from two efficacy studies, FS-67-E01 and FS-67-E02. Study FS-67-E01 was a pilot trial to gather useful information, and Study FS-67-E02 was the confirmatory superiority trial. I only reviewed the latter study.

Study FS-67-E02 was a 12-hour, double-blind, placebo-controlled, multi-center study to investigate the safety and analgesic effect of FS-67 topical patch in subjects with muscle strain. In the study, 208 patients were randomized to FS-67 topical patch single dose (n = 105) or placebo topical patch single dose (n = 103) in a 1:1 ratio. The primary efficacy outcome variable was SPID8 with movement. Secondary efficacy variables were SPID8 at rest, TOTPAR8 with movement or at rest, PID with movement over several assessment time points, onset of analgesia (perceptible and meaningful pain relief) based on double stopwatches, and subject global satisfaction.

1.3 Statistical Issues and Findings

The sponsor's pre-specified primary analysis employed an analysis of variance model with terms for treatment and center. Two centers were pooled because of too few subjects. I additionally conducted an analysis without pooling the two centers, and I conducted an analysis utilizing an analysis of covariance model with terms for treatment, center and baseline pain score as covariate.

The sponsor proposed a last observation carried forward (LOCF) strategy to impute missing data in the primary analysis. The sponsor also used a worst observation carried forward (WOCF) imputation strategy as a sensitivity analysis. However, missing data was not an issue due to an unusually low dropout rate which was less than 1 %.

Based on my review of study results, I conclude that the results of the study seem to confirm the analgesic efficacy of FS-67 compared to placebo as measured by the SPID8 with movement. Support for the primary findings was additionally gained from several secondary variables. Specifically, I found that the study showed significant differences between FS-67 and placebo in the SPID8 at rest, TOTPAR8 with movement, TOTPAR8 at rest, and PID with movement over 1 to 8 hours. However, there were no significant differences in the time to onset of both perceptible and meaningful pain relief between FS-67 and placebo.

2. INTRODUCTION

2.1 Overview

2.1.1 Drug class and regulatory history

Salonpas® and La-Salonpas® are two marketed over-the-counter patch formulations used for the relief of minor aches and pains of muscles and joints. According to Hisamitsu, they have developed a new topical formulation, referred to as FS-67, containing the same active counter-irritant ingredients as Salonpas and similar active ingredients to Dories. The sponsor states,

> FS-67 differs from Salonpas in two ways. FS-67 contains 10% MS [redacted] and 3% LM [redacted] and it is formulated with [redacted] backing. Also, the size of the patch, 70 cm^2, is wider than Salonpas, 27.3 cm^2. FS-67 is the same size and has the same composition as Dories except for some inactive ingredients. b(4)

The proposed trade name is Salonpas® [redacted] The sponsor introduced FS-67 to the agency via IND 62, 735. During drug development, the product was discussed at a pre-IND meeting and a pre-NDA meeting. Issues discussed at the meetings included the need for various non-clinical studies, the adequacy of the proposed pain model and endpoints, the use of a single-dose study, and the appropriateness of the planned analyses. In addition, a special protocol was submitted on September 7, 2004, and amended protocols were submitted in December of 2004 and March of 2005. The statistical reviewer of the amended protocols, Atiar Rahman, recommended additional sensitivity analyses with respect to the handling of missing data. b(4)

Of note, a tentative final monograph (TFM) for OTC External Analgesic Drug Products (48 FR 5852) exists that provides for topically applied ointments (or lotions or creams) containing methyl salicylate and l-menthol; however, the monograph does not contain a topical patch. The sponsor states,

The TFM notes the following uses: "For the temporary relief of minor aches and pains of muscles and joints" which may be followed by: "associated with" [select the following: "simple backache," "arthritis", "strains", "bruises" and "sprains"]. The FDA suggested that Hisamitsu select 1 of these indications for evaluation of pain relief. The FDA proposed a pilot study to enable the estimation of sample size for the pivotal, registration trials with FS-67. Initially, the FDA agreed that a study of analgesic onset with 8 hours of evaluation was adequate for the assessment of the efficacy of FS-67; the pilot study used an 8-hour evaluation period. Subsequently, the FDA suggested maintaining the treatment period at 8 hours but extending the observation period to 12 hours to obtain data on duration of effect. The current study used an observation period of 12 hours.

2.1.2 Proposed Indication for Salonpas® [redacted]

Salonpas® [redacted] (FS-67 topical patch) is indicated for the temporary relief of mild to moderate aches and pains of muscles and joints associated with arthritis, simple backache, strains, bruises and sprains. b(4)

2.2 Data Sources

NDA 22-029 was submitted on February 27, 2006 and can be found in the FDA, CDER document room. The electronic SAS data sets were submitted on February 27, 2006 and June 13, 2006 and can be found in the FDA, CDER electronic document room (EDR) using the following paths:

\\CDSUB1\N22029\N_000\2006-02-27
\\CDSUB1\N22029\N_000\2006-06-13

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study FS-67-E02 was a 12-hour, multi-center, double-blind study of the safety and efficacy of FS-67 topical patch compared to placebo patch in subjects with muscle strain. Two-hundred and eight eligible patients were randomized to FS-67 or placebo in 1:1 ratio at 15 sites. Figure 5 in the appendix shows a schematic of the study design.

The sponsor defined the primary efficacy endpoint as the summed pain intensity difference at 8 hours (SPID8) with movement. SPID8 was a time-weighted sum of pain and was calculated using the following formula:

$$SPID8 = \frac{1}{2} PID0.5 + \frac{1}{2} PID1 + PID2 + \ldots + PID8$$

where PIDi denoted the pain intensity difference at hour i. The pain intensity difference (PID) was calculated using the following formula:

PIDi =pain intensity at baseline – pain intensity at hour i

Pain intensity was measured using a visual analog scale (VAS) that ranged from 0 ("no pain") to 100 ("extreme pain") in mm.

The secondary efficacy variables included SPID8 at rest, total pain relief at 8 hours (TOTPAR8) with movement and at rest, PID with movement over assessment time points, onset of analgesia (perceptible and meaningful pain relief) based on double stopwatches, and subject global satisfaction.

3.1.2 Patient Disposition and Demographics

As shown in Table 10 in the appendix, about 1% of the patients discontinued from study FS-67-E02. Since this dropout rate was unusually low, imputation of missing data was not an issue.

Table 11 in the appendix shows patient demographics by treatment group. There were no noticeable imbalances among treatment groups with respect to the demographic variables of age, race, and weight. The table also shows baseline values for the pain VAS score by treatment group. Mean baseline values for the pain VAS scores were comparable between treatment groups.

3.1.3 Statistical Methodologies

The primary efficacy outcome was compared between FS-67 topical patch and placebo using an analysis of variance (ANOVA) model with terms for treatment and center. Two centers, center 04 and center 13, were pooled because of too few subjects. A similar ANOVA model was used to analyze SPID at rest, PID with movement at each assessment time point, and TOTPAR at each assessment time point. In addition, Kaplan-Meier curves and log-rank tests were used to analyze the time to onset of perceptible pain relief and the time to onset of meaningful pain relief.

The primary analysis was conducted on the intent to treat population including all randomized patients who received study drug. Missing data was imputed using a last observation carried forward (LOCF) strategy. An additional sensitivity analysis used a worst observation carried forward (WOCF) strategy to impute missing data.

3.1.4 Results and Conclusions

Tables 1 – 9 and Figures 1 – 4 present the statistical analyses done by the sponsor and me. The following are the results of the analyses.

In the study, a greater analgesic effect (as measured by SPID8 at movement) was achieved by the FS-67 topical patch as compared to the placebo patch. The sponsor's primary and sensitivity analyses both demonstrated superiority of FS-67 topical patch to placebo. I additionally performed an analysis of covariance with treatment and center as factors and baseline pain as a covariate the analysis. My results were consistent with those of the sponsor.

While secondary variables were evaluated, no adjustments were made to address multiplicity concerns arising from the testing of several secondary outcomes. Significant differences between treatment and placebo were evident in the SPID8 at rest, TOTPAR8 with movement and TOTPAR8 at rest. The pain intensity difference with movement was significantly different between FS-67 and placebo over the 1 to 8 hours period. However, there were no significant differences in the time to onset of perceptible pain relief or on time to onset of meaningful pain relief between FS-67 topical patch compared to placebo patch.

Table 1 Sponsor's Primary Efficacy Analysis (SPID8 with Movement): ITT LOCF

SPID8 WITH MOVEMENT		
	FS-67 (N=105)	**PLACEBO (N=103)**
LSMean (SE)	189.6 (13.2)	137.5 (13.3)
Diff. from PBO (95% CI)	52.1 (16.2, 88.0)	
p-value	.0047	

LSMeans and p-values calculated from ANOVA model: Y = trt + center.

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Table 2 Sponsor's Sensitivity Analysis (SPID8 with Movement): ITT WOCF

SPID8 at Movement		
	FS-67 (N=105)	**PLACEBO (N=103)**
LSMean (SE)	189.1 (13.2)	137.6 (13.3)
Diff. from PBO (95% CI)	51.5 (15.6, 87.5)	
p-value	.0052	

LSMeans and p-values calculated from ANOVA model: Y = trt + center.

Table 3 Reviewer's Sensitivity Analysis (SPID8 with Movement): ITT LOCF ANCOVA

SPID8 WITH MOVEMENT		
	FS-67 (N=105)	**PLACEBO (N=103)**
LSMean (SE)	190.8 (12.9)	136.5 (13.3)
Diff. from PBO (95% CI)	54.3 (19.1, 89.6)	
p-value	.0027	

LSMeans and p-values calculated from ANCOVA model: Y = trt + center + baseline pain.

Table 4 Sponsor's Time-specific Analysis of PID with Movement: ITT LOCF

TIME POINT	FS-67 MEAN (SE)	PLACEBO MEAN (SE)	P-VALUE
Baseline Pain Severity	64.7 (0.8)	65.3 (0.7)	0.567
PID at 30 minutes	6.3 (1.0)	4.4 (1.1)	0.206
PID at 1 hour	11.4 (1.4)	6.3 (1.4)	0.010
PID at 2 hour	16.2 (1.7)	11.5 (1.6)	0.041
PID at 3 hour	21.7 (1.8)	15.4 (1.0)	0.016
PID at 4 hour	24.6 (1.0)	16.6 (2.2)	0.005
PID at 5 hour	25.6 (2.0)	17.6 (2.0)	0.004
PID at 6 hour	27.5 (2.0)	19.0 (2.1)	0.003
PID at 7 hour	28.5 (2.1)	21.8 (2.3)	0.026
PID at 8 hour	29.7 (2.2)	22.7 (2.4)	0.028
PID at 9 hour	29.5 (2.4)	23.8 (2.5)	0.091
PID at 10 hour	29.8 (2.4)	23.6 (2.5)	0.073
PID at 11 hour	30.6 (2.5)	23.7 (2.5)	0.044
PID at 12 hour	31.1 (2.4)	24.2 (2.5)	0.044

P-values calculated from ANOVA model: Y = trt + center.

Table 5 Sponsor's Secondary Efficacy Analysis (SPID8 at Rest): ITT LOCF

SPID8 AT REST		
	FS-67 (N=105)	**PLACEBO (N=103)**
LSMean (SE)	156.5 (12.9)	118.0 (13.0)
Diff. from PBO (95% CI)	38.5 (3.4, 73.6)	
p-value	.0316	

LSMeans and p-values calculated from ANOVA model: Y = trt + center.

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Table 6 Sponsor's Secondary Efficacy Analysis (TOTPAR8 with Movement): ITT LOCF

TOTPAR8 WITH MOVEMENT		
	FS-67 (N=105)	**PLACEBO (N=103)**
LSMean (SE)	12.3 (0.7)	9.4 (0.7)
Diff. from PBO (95% CI)	3.0 (1.1, 4.9)	
p-value	.0022	

LSMeans and p-values calculated from ANOVA model: Y = trt + center.

Table 7 Sponsor's Secondary Efficacy Analysis (TOTPAR8 at Rest): ITT LOCF

TOTPAR8 AT REST		
	FS-67 (N=105)	**PLACEBO (N=103)**
LSMean (SE)	12.3 (0.7)	9.8 (0.7)
Diff. from PBO (95% CI)	2.5 (0.5, 4.5)	
p-value	.0166	

LSMeans and p-values calculated from ANOVA model: Y = trt + center.

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Table 8 Sponsor's Secondary Efficacy Analysis (Time to Perceptible Pain Relief): ITT

Time to Perceptible Pain Relief		
	FS-67 (N=105)	**PLACEBO (N=103)**
Median (hr)	2.50	3.17
p-value	.127	

P-value was based on log-rank test.

Table 9 Sponsor's Secondary Efficacy Analysis (Time to Meaningful Pain Relief): ITT

Time to Meaningful Pain Relief		
	FS-67 (N=105)	**PLACEBO (N=103)**
Median (hr)	13.17	12.42
p-value	.472	

P-value was based on log-rank test.

Figure 1 Reviewer's Display of Treatment*Center Interaction Effect: ITT LOCF (p=.1221)

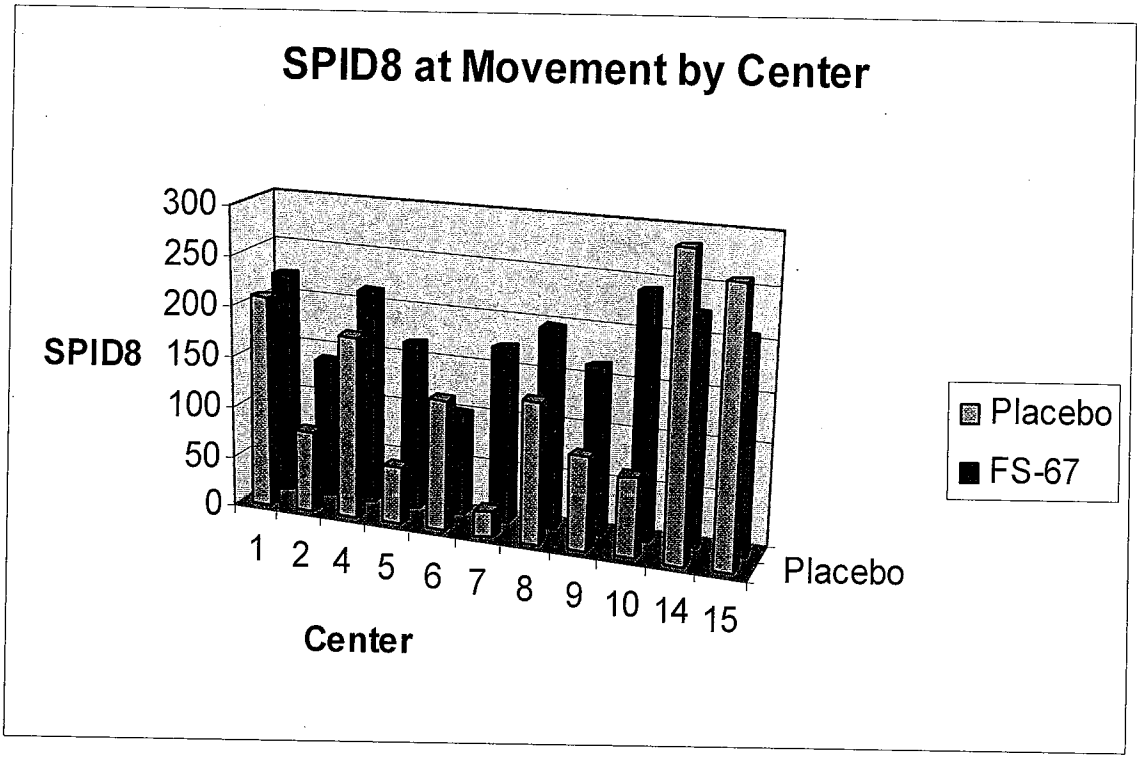

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Figure 2 Sponsor's Time-specific Analysis of PID with Movement: ITT LOCF

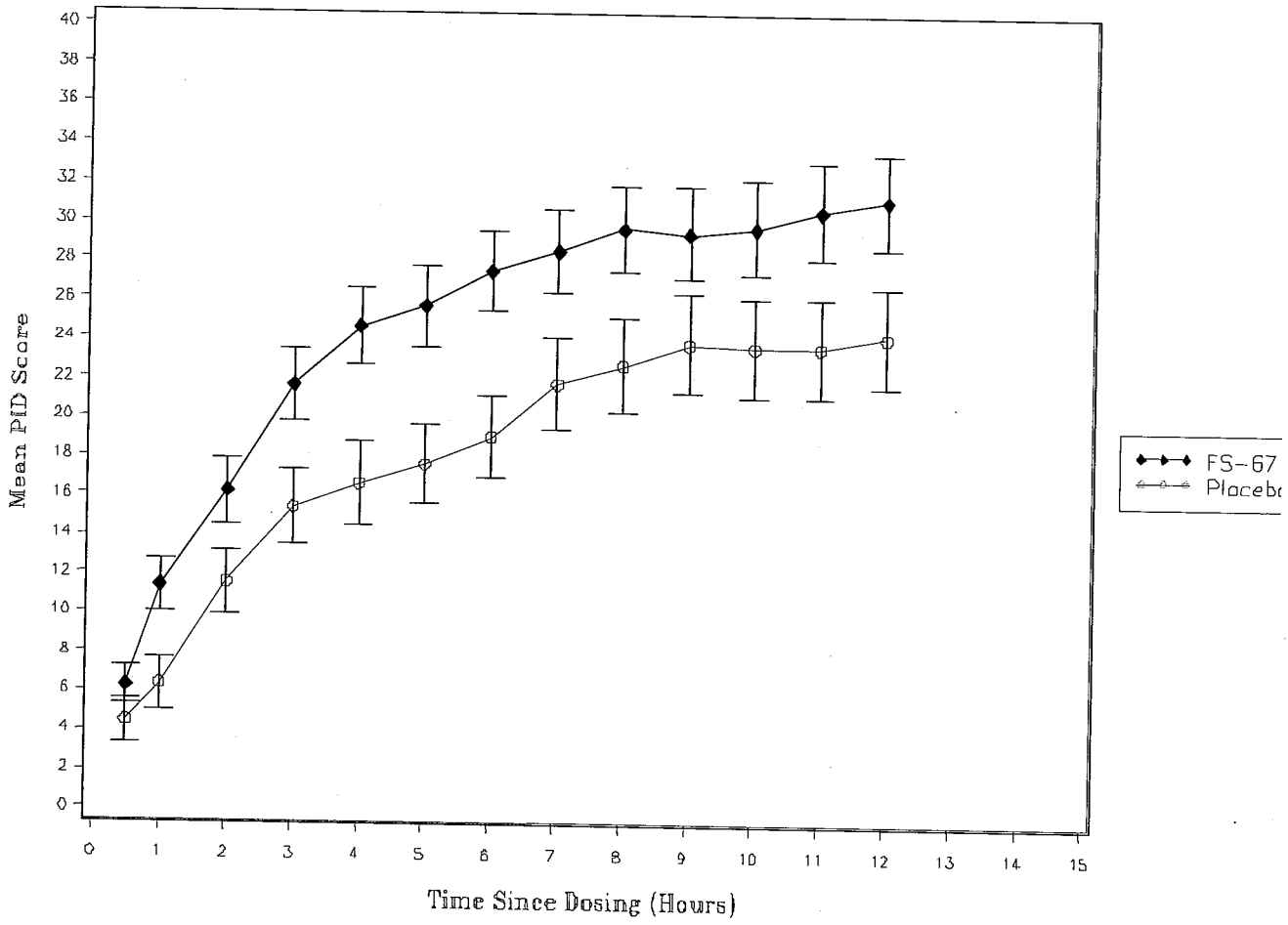

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Figure 3 Sponsor's Analysis of Time to Perceptible Pain Relief: ITT

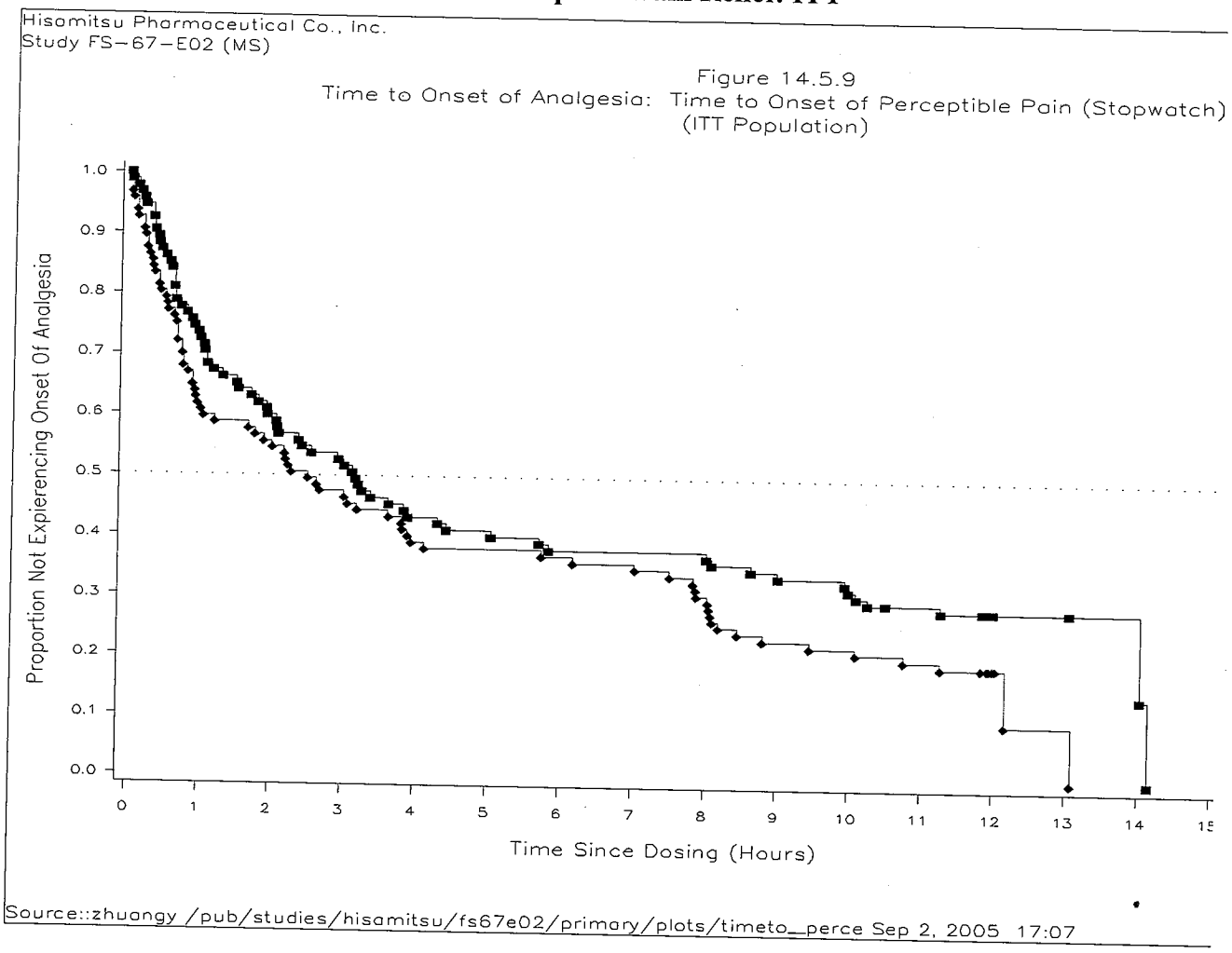

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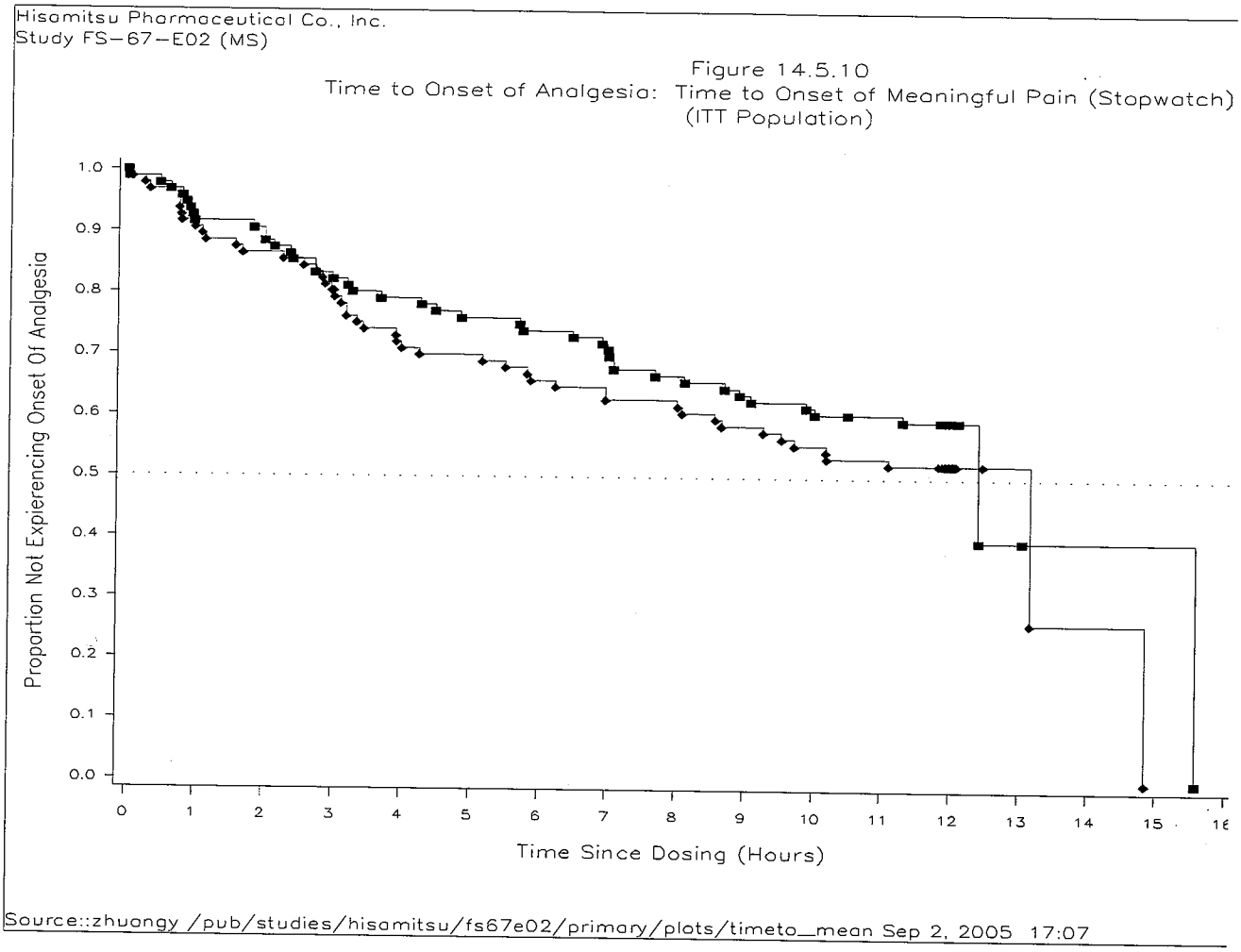
Figure 4 Sponsor's Analysis of Time to Meaningful Pain Relief: ITT



3.2 Evaluation of Safety

Safety analyses were done by clinical reviewer, Joseph Porres, M.D.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor explored the heterogeneity of the treatment effect across age, race, and gender by inclusion of interaction terms in the ANOVA model. In the analyses, there were no statistically significant interactions between treatment and age ($\leq$ 40 yr. vs. > 40 yr.), gender,

or race in the SPID8 with movement. The sponsor did not propose any efficacy claims for any subgroups of patients.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Statistical Issues

The sponsor's pre-specified primary analysis employed an analysis of variance model with terms for treatment and center. Two centers were pooled because of too few subjects. I additionally conducted an analysis without pooling the two centers, and I conducted an analysis utilizing an analysis of covariance model with terms for treatment, center and baseline pain score as covariate.

The sponsor proposed a last observation carried forward (LOCF) strategy to impute missing data in the primary analysis. The sponsor also used a worst observation carried forward (WOCF) imputation strategy as a sensitivity analysis. However, missing data was not an issue due to an unusually low dropout rate which was less than 1 %.

5.1.2 Collective Evidence

I reviewed the sponsor's single efficacy study. In reviewing the collective evidence from the sponsor's analyses as well as my additional analyses, I conclude that the data from the study seem to confirm the analgesic efficacy of FS-67 compared to placebo as measured by the summed pain intensity difference. However, the study failed to show superiority of FS-67 over placebo in terms of the time to onset of analgesia.

5.2 Conclusions and Recommendations

Study FS-67-E02 was conducted in subjects with muscle strain and demonstrated a statistically significant difference in the summed pain intensity difference with movement from baseline to hour 8 between the FS-67 topical and placebo patches.

The study additionally showed significant differences between the treatment and placebo on several secondary efficacy outcome variables including SPID8 at rest; total pain relief with movement and at rest at Hour 8, and pain intensity difference with movement over 1 to 8 hours. In contrast, there were no differences in the time to onset of perceptible pain relief and in the time to onset of meaningful pain relief.

Overall, the study was successful in showing superiority of FS-67 topical patch over placebo in terms of pain reduction in the acute setting. However, the study failed to provide evidence of superiority of FS-67 in terms of the time to onset of analgesia, a measure of clinical interest.

5.3 Review of Clinical Studies of Proposed Label

Since the FS-67 topical patch is targeted for the over-the-counter (OTC) market, only the 'Drug Fact' portion of the product box is provided for review, and this does not contain any of the clinical trial results.

APPENDIX

Table 10 Patient Disposition by Treatment Group

Study FS-67-E02:

	FS-67	PLACEBO
Randomized	105	103
ITT	105	103
PP	92	96
Completers	104 (99%)	102 (99%)
Dropouts	1 (1%)	1 (1%)
AE	1 (1%)	0 (0%)
LOE	0 (0%)	1 (1%)

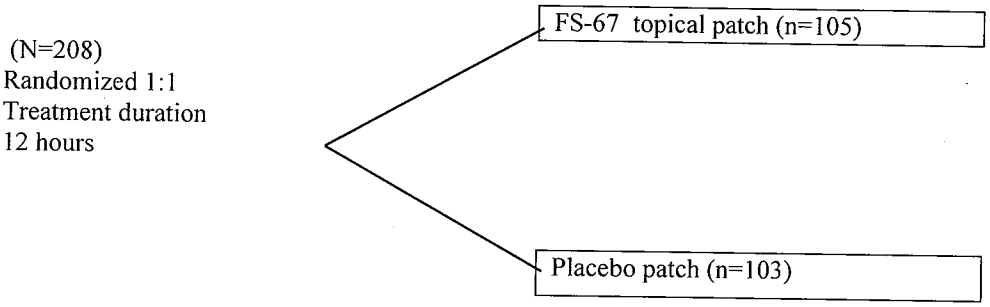
Table 11 Patient Demographics and Baseline Efficacy Variable (ITT Population)

Study FS-67-E02:

	FS-67 (n=105)	**Placebo (n=103)**
Gender n (%)		
Male	50 (48%)	54 (52%)
Female	55 (52%)	49 (48%)
Race n (%)		
Asian	0 (0%)	0 (0%)
Black	29 (28%)	27 (26%)
Caucasian	53 (50%)	49 (48%)
Hispanic	22 (21%)	26 (25%)
Other	1 (1%)	1 (1%)
Age (years)		
Mean ± SD	37.3 ± 13.2	38.1 ± 13.4
Median	35.0	36.0
Range	18.0 – 72.0	18.0 – 78.0
Weight (kg)		
Mean ± SD	83.4 ± 19.4	81.0 ± 18.3
Median	81.4	81.1
Range	50.5 – 138.2	45.2 – 145.5
Baseline Pain Severity		
Mean ± SE	64.7 ± 0.8	65.3 ± 0.7

Figure 5 Schematic of Study Design

Study FS-67-E02:



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