

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-612

STATISTICAL REVIEW(S)

550 Koerner

Statistical Review and Evaluation

NDA: 20-612
Drug Name: Lidoderm (lidocaine patch)
Applicant: Hind Health Care
Statistical Reviewer: Richard A. Stein, PhD
Submission Date: 6/11/96
Review #1 Dated: December 3, 1996
Reviewing Medical Officer: Rosemarie Neuner, MD
Volumes Reviewed: 2.07-2.10
Indication: Symptomatic Relief of Postherpetic Neuropathy Pain

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I. Background

This submission consists of two studies done under Michael Rowbotham, MD. The first was a phase II, 4-period crossover study in 35 evaluable patients. The second was a phase III two-center parallel group study in 150 evaluable patients.

II. Study Design

Study number one was a phase II, 4-period double-blind crossover study in 35 evaluable patients. Treatment periods involved of a vehicle patch period, a no-treatment period, and two lidocaine patch periods randomized in accordance with a crossover design. The protocol does not clearly identify primary efficacy pain scales. Submitted were data analyses for Pain Intensity, Pain Relief, sensitivity to hot and cold stimuli and check list side effects. The protocol did not mention the allodynia scale which was submitted to this reviewer in electronic data format along with the other pain data. The protocol descriptions of the statistical analyses are unclear. The study takes place over a period of at most 42 days. Each pain evaluation session involves a 6-hour in-clinic evaluation and a 6-hour pain evaluation at home. Baseline pain is recorded twice with a 15 minute gap. Then the in-clinic data was to be recorded at 30 minutes and 1, 2, 3, 4, 6 hours. The home evaluation took place 9 and 12 hours after patch application.

The second study was a randomized, parallel group, double-blind phase III study in 150 evaluable patients conducted in two 10-hour sessions at least 48 hours apart. Treatments consisted of a lidocaine patch and a vehicle patch randomized in a 2:1 ratio. Each pain evaluation session involves a 6-hour in clinic evaluation and a 4-hour pain evaluation at home. Baseline pain is recorded twice with a 15 minute gap. Then the in-clinic data is recorded at 1, 2, 4, 6 hours. The home evaluation took place 8 and 10 hours after patch application. The statistical analysis was to follow an ANOVA modeling involving treatment, center, and treatment-by-center interaction.

III. Statistical Methods and Results

In the phase II study, the sponsor used a conventional ANOVA analysis of the original data or of difference from average baseline when a baseline was available. Statistically significant differences were found between lidocaine patch and vehicle patch on the pain intensity scale at hours 4, 6, 8, and 12 as well as averaged across all seven pain evaluation times. No satisfactory statistical results were obtained for 30 minutes, and for hours 1 and 2. For pain relief, only marginal statistical differences ($0.05 < p \leq 0.10$) were found at hours 6, 9, and 12. No satisfactory statistical results were obtained for 30 minutes, and for hours 1, 2, 3, and 4. However, averaging the results for all observation times led to a statistically significant result favoring lidocaine patch over placebo.

In the phase III study, the sponsor used a conventional ANOVA analysis of the original data or of difference from average baseline when a baseline was available. The sponsor reported only average results (Vol. 2.10, page 2240). As seen in the appendix, this may be because individual hour-by-hour results are disappointing. Essentially, this study shows efficacy only for allodynia, but not for the pain intensity and pain relief scales. Allodynia, while perhaps important, is not an efficacy variable identified in the protocol.

IV. Reviewer's Conclusions

1. In the phase II study, statistical evidence of efficacy has been shown for the pain intensity scale at hours 4, 6, 8, and 12 as well as averaged across all seven pain evaluation times. No statistical evidence of efficacy has been shown at 30 minutes, or for hours 1 and 2. On the pain relief scale, statistical evidence of efficacy was shown when averaged across all seven pain evaluation times. At individual time points, at best marginal statistical differences in pain relief ($0.05 < p \leq 0.10$) were found at hours 6, 9, and 12.
2. In the phase III study, statistical evidence of efficacy was shown for the allodynia scale, but not for the pain relief or pain intensity scales. This result for allodynia can be considered an exploratory result since allodynia was not identified as an efficacy variable in the protocol.

JSI

Richard A. Stein, Ph.D.
Mathematical Statistician

Concur:

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Team Leader

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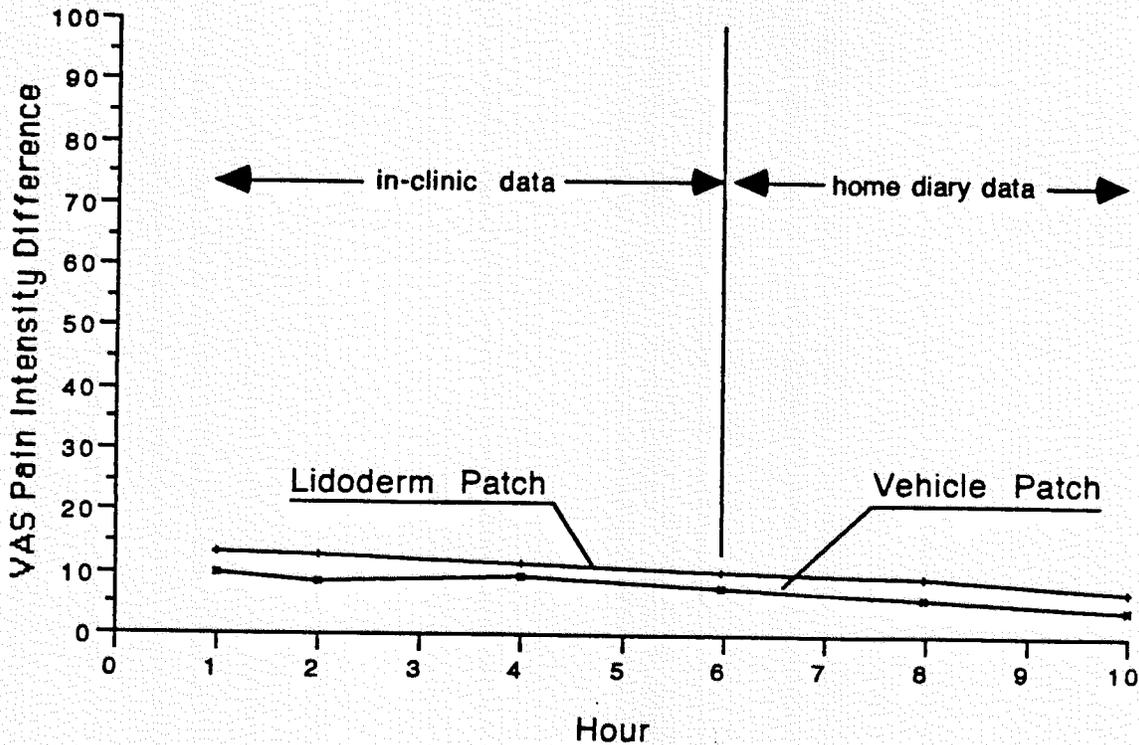
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Archival: NDA 20-612
HFD-550/Division File
HFD-550/MO/Rosemarie Neuner, MD
HFD-550/PM/C. - Koerner
HFD-340/Div. Sci. Inv.
HFD-725/Division File
HFD-725/Stat/Richard Stein, PhD

Appendix

The sponsor did not graph the time evolution of either the Phase II or the Phase III study. Below, this reviewer has graphed the VAS pain intensity differences averaged over treatment sessions 1 and 2 and verified the applicant's p-values for the Phase III study. The session average is used for simplicity because the results for sessions 1 and 2 are quite similar. As is common practice, the graph scale of the results goes to the maximum pain intensity difference achievable.

VAS Pain Intensity Difference
Average of Sessions 1 and 2



**Reviewer's Computed Pain Intensity, Pain Relief and Allodynia Results
for Lidoderm Phase III Trial**

Summary of P-Values for VAS Pain Intensity

Hour	ANOVA		ANCOVA	
	Session 1	Session 2	Session 1	Session 2
1	0.64	0.10	0.52	0.09
2	0.55	0.03	0.40	0.03
4	0.96	0.19	0.87	0.17
6	0.93	0.22	0.76	0.20
8	0.49	0.27	0.29	0.21
10	0.89	0.18	0.70	0.16
Avg.	0.69	0.11	0.47	0.09

Summary of P-Values for Pain Relief

Hour	ANOVA	
	Session 1	Session 2
1	0.85	0.41
2	0.51	0.13
4	0.39	0.14
6	0.96	0.18
8	0.24	0.20
10	0.04	0.16
Avg.	0.33	0.17

Summary of P-Values for Allodynia

Session 1	Session 2	Averaged
0.01	0.02	0.01

**APPEARS THIS WAY
ON ORIGINAL**

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-612/Drug Class 3S
APPLICANT: Hind Health Care, Inc.
NAME OF DRUG: Lidoderm™ (Lidocaine) DDS (dermal delivery system)
INDICATION: Treatment of pain in Post-Herpetic Neuralgia (Shingles)
DOCUMENTS REVIEWED: Vol. 6.1- 6.5 dated June 02, 1998
Amendment dated October 14, 1998
MEDICAL REVIEWER: Christina Fang, MD (HFD-550).

I. Background & Summary

The NDA 20-612 was originally Not Approved because of various deficiencies. Consequently, a meeting was held between the sponsor and the FDA on July 21, 1997. During the meeting, the FDA stated that additional clinical data would be necessary before reconsideration of NDA 20-612 for approval. Hence, in this NDA, the sponsor has submitted results of one study seeking approval of Lidoderm™ DDS for the treatment of pain in Post-Herpetic Neuralgia (PHN).

II. Sponsor's Study Design, Analyses, Results

Objectives: The purpose of this double-blind, placebo-controlled, cross-over study was to test the analgesic efficacy of Lidoderm™ DDS compared to the placebo DDS (without lidocaine) in the treatment of pain in PHN.

Design: This was a double-blind, balanced random assignment, placebo (vehicle) controlled, cross-over trial of 28 days maximum duration, with as many as 14 days of treatment by patients at home with each blinded test article (active or vehicle) without in between washout. Half of the subjects were randomized to receive the active agent as the first treatment and half received placebo (vehicle) as the first treatment. This crossover design utilized an "enriched" population of patients who have already been deriving pain relief from Lidoderm™ DDS in an open label fashion. The primary measure was "time to exit" comparing treatment phases, while the secondary outcome measure was patient preference between treatment phases. Patients' average pain relief was scored through daily telephone interviews. They were asked to score their average pain relief on a 6-point categorical scale: worse, no pain relief, slight relief, moderate relief, a lot of relief and complete relief.

Primary Efficacy Variable: Time to exit, paired comparison of treatment time spent in each treatment phase.

Time to Exit: The subject used the blinded test article in the same manner as open-label Lidocaine DDS for up to 14 days for each treatment phase. The subject was allowed to exit either treatment phase if the verbal pain relief rating decreased as much as 2 categories for any 2 consecutive days, when compared to their normal open-label experience ("a lot" during open-label use became "slight" during a treatment phase, or, "complete relief" was changed to "moderate" or less).

Secondary Efficacy Variable: Patient assessment of the treatment phase providing the greatest benefit.

Statistical Methods: The study exit times were analyzed with an analysis of variance (ANOVA) to determine if the sequence of administration (Lidocaine DDS first or second) had any effect on the efficacy outcome of study exit time. The ANOVA model included sequence, patients nested within sequence, period, and treatment groups as factors. The significance of the sequence effect was tested using the patients nested within sequence as the error term.

The data of the first period only was analyzed for efficacy to evaluate the difference between treatment groups if the sequence effect was statistically significant. Otherwise, the data from the complete crossover was used to determine the difference between treatment groups using each patient as their own control in the stratified analysis of study exit time.

As described in the protocol, the analysis of time to study exit used the Wilcoxon test, survival techniques stratified by patient for the purpose of comparing exit time distributions across the treatment groups. In the study exit time analysis, an observation was considered censored at 14 days if the study exit had not occurred before the end of the 14 day study period. The median time and 95% confidence limits for the median were also calculated (in days) for each of the treatment groups without stratification.

Patient Disposition: The protocol did not provide calculations regarding sample size. But, in Appendix 16.1.3 (page 082) in the Consent Form, it was stated that approximately 50 subjects would participate in this study. However, only thirty-three patients were enrolled and randomized. One patient suffered a disabling stroke prior to receiving treatment and could not participate. Of the remaining 32 patients, 2 were discontinued early during phase B (placebo in both cases). All 32 patients were included in the analyses.

It is not clear to this reviewer how the sponsor stopped at 33 patients instead of enrolling up to 50 patients.

Efficacy Results: The sequence analysis for the study exit time is displayed in Table 1 in the Appendix. Sequence of administration had no effect on the efficacy outcome of study exit time ($p=0.6885$). This sequence analysis is the standard test for carryover effects in a crossover study design. The results of survival analysis are displayed in Figure 1 in the Appendix. The median times to exit were >14 days for Lidoderm and 3.8 days for placebo. Statistical significance was achieved between treatments ($p<0.001$) utilizing Wilcoxon test.

III. FDA-Requested Analyses

During a telephone conference call on October 9, 1998, the FDA requested the following data analyses regarding this study:

- Survival Analysis of Time to Exit: Combined Periods, First Period Only, Second Period Only
- Mean Pain Relief Scores: Combined Periods, First Period Only, Second Period Only
- Use of Concomitant Analgesic Medications: Combined Periods, First Period Only, Second Period Only.

The sponsor responded and submitted an amendment on October 14, 1998 that included results of the above analyses. This reviewer was able to reproduce the sponsor's results.

Survival Analysis of Time-to-Exit: For the primary efficacy variable of Time-to-Exit, on FDA's request, the sponsor submitted two analyses for the two periods separately. These are included as Figure 1.1 and 1.2 in the Appendix. In Figure 1.1 (First Period Data Only), the median times to exit were >14 days for Lidoderm and 2.7 days for placebo. Statistical significance was achieved between treatments ($p<0.001$) utilizing Wilcoxon test. In Figure 1.2 (Second Period Data Only), the median times to exit were >14 days for Lidoderm and 6.0 days for placebo. Statistical significance was achieved between treatments ($p<0.001$) utilizing Wilcoxon test, for both periods.

Mean Pain Relief Scores: Mean values, standard errors, and 95% confidence intervals for the relief scores of each treatment were computed for each treatment day. In this intent-to-treat analysis, the last relief observation was carried forward to the 14th day. Results are included in the Appendix. Table 2 displays pain relief scores through time for both treatment periods combined, whereas Tables 2.1 and 2.2 display relief scores for each treatment period separately. Figures 2, 2.1 and 2.2 are the graphical representations of Tables 2, 2.1 and 2.2 respectively. These analyses show the improvement in relief for the Lidoderm.

Use of Concomitant Analgesic Medications: Tables 3, 3.1 and 3.2 (in the Appendix) display an analysis of concomitant medications used by patients for

both periods combined, and for the first and second treatment periods separately. The numbers listed are the number of days that patients used *any* type of analgesic medication including acetaminophen, NSAIDs, opioids, and tricyclic antidepressants. In addition, the sponsor included the number of days the subjects remained in each treatment period, and also the ratio of the number of days of concomitant drugs to the number of days in the study periods. With regard to this ratio, there is no apparent difference in the frequency of concomitant medication use during active or placebo treatment.

IV. Statistical Reviewer's Conclusions

This NDA was originally Not Approved because of a lack of demonstrated efficacy and various other deficiencies. Consequently, a meeting was held between the sponsor and the FDA on July 21, 1997. During the meeting, the FDA stated that additional clinical data would be necessary in order to reconsider this NDA for approval. Hence, in this NDA, the sponsor has submitted results of one study seeking approval of Lidoderm™ DDS for the treatment of pain in Post-Herpetic Neuralgia (PHN).

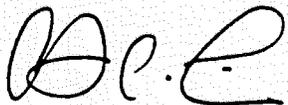
In this study, the crossover design utilized an "enriched" population of patients who have already been deriving pain relief from Lidoderm™ DDS. On the basis of pain relief scores, patients on Lidoderm appeared to continue to derive pain relief whereas placebo patients did not. This design presupposes the efficacy of Lidoderm™ DDS.

Statistical analysis of the intent-to-treat dataset in this study demonstrated statistically significant difference ($p < 0.001$) between Lidoderm™ DDS and placebo for the primary efficacy variable of "time to exit" favoring Lidoderm in both the periods separately as well as combined periods.

The sponsor did not provide any details of sample size calculations in the protocol. However, the sponsor planned to enroll approximately 50 patients for this study, but enrolled only 33 patients. It is not clear to this reviewer how the sponsor stopped at 33 patients instead of enrolling up to 50 patients as planned. Did the sponsor conduct an interim analysis? If yes, there are no details of it in the NDA submission. This causes a serious concern regarding the reliability of the results of this study.

ISI

Baldeo K. Taneja, Ph.D.
Mathematical Statistician (Biomed)



Concur: Dr. Stan Lin

11/18/98

cc:

Archival NDA # 20-612
HFD-550/Division File
HFD-550/DeLap
HFD-550/Fang
HFD-550/Lutwak
HFD-725/Taneja
HFD-725/LinSt
HFD-725/Huque
HFD-725/Chron

This review contains 18 pages: 5 pages of text and 13 pages of Appendix containing Tables (1, 2, 2.1, 2.2, 3, 3.1 and 3.2) and Figures (1, 1.1, 1.2, 2, 2.1 and 2.2).

TABLE 1

Sequence Analysis for Time to Exit

General Linear Models Procedure

Class Level Information

Class	Levels	Values
RXCODEN	2	1 2
SEQ	2	1 2
PERIOD	2	1 2

Number of observations in data set = 64

General Linear Models Procedure

Dependent Variable: STUDY EXIT TIME

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	5	758.8196018	151.7639204	8.92	0.0001
Error	58	986.2897732	17.0049961		
Corrected Total	63	1745.1093750			

R-Square	C.V.	Root MSE	BKTIME Mean
0.434826	40.54033	4.123711	10.1718750

Source	DF	Type I SS	Mean Square	F Value	Pr > F
RXCODEN	1	534.7656250	534.7656250	31.45	0.0001
SEQ	1	8.2656250	8.2656250	0.49	0.4885
PERIOD	1	107.6406250	107.6406250	6.33	0.0147
PTID(SEQ)	2	108.1477268	54.0738634	3.18	0.0489

Source	DF	Type III SS	Mean Square	F Value	Pr > F
RXCODEN	1	534.7656250	534.7656250	31.45	0.0001
SEQ	1	11.6181511	11.6181511	0.68	0.4119
PERIOD	1	107.6406250	107.6406250	6.33	0.0147
PTID(SEQ)	2	108.1477268	54.0738634	3.18	0.0489

Tests of Hypotheses using the Type III MS for PTID(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	11.61815108	11.61815108	0.21	0.6885

TABLE 2
PAIN RELIEF SCORES (Combined Periods)

<u>UCL</u> ^a	<u>ACTIVE</u> <u>Mean (LCL, UCL)^a</u>	<u>PLACEBO</u> <u>Mean (LCL,</u>
Number of Subjects ^b	31	31
Relief Scores		
Day 1	4.6 (4.3, 5.0)	3.1 (2.6, 3.6)
Day 2	4.5 (4.2, 4.8)	3.3 (2.8, 3.8)
Day 3	4.6 (4.3, 4.9)	3.1 (2.7, 3.6)
Day 4	4.6 (4.3, 4.9)	3.1 (2.6, 3.6)
Day 5	4.4 (4.1, 4.8)	3.1 (2.7, 3.6)
Day 6	4.5 (4.2, 4.8)	2.9 (2.5, 3.3)
Day 7	4.4 (4.0, 4.8)	3.1 (2.6, 3.6)
Day 8	4.5 (4.2, 4.9)	3.1 (2.7, 3.6)
Day 9	4.4 (4.1, 4.8)	3.0 (2.6, 3.5)
Day 10	4.5 (4.2, 4.9)	3.0 (2.6, 3.5)
Day 11	4.5 (4.2, 4.9)	3.1 (2.6, 3.6)
Day 12	4.6 (4.2, 5.0)	3.1 (2.6, 3.5)
Day 13	4.5 (4.1, 4.9)	3.2 (2.7, 3.7)
Day 14	4.5 (4.1, 4.8)	3.2 (2.7, 3.7)

^a (LCL, UCL) equals 95% lower and upper confidence limit.

^b Sample size is decreased by one subject due to Subject 156 not recording daily diary relief scores.