CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-486

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-486

Drug Name: Lidopel (2% Lidocaine HCl and Epinephrine 1:100,000)

Indication(s): [redacted]

Applicant: Empi Corp.

Date(s): Submitted 9/26/03

Review Priority: Standard

Biometrics Division: Division of Biometrics 2 (HFD-715)

Statistical Reviewer: Lisa A. Kammerman, Ph.D.

Concurring Reviewers: N/A

Medical Division: Division of Anesthetics, Critical Care and Addiction Drug Products.

Clinical Reviewer: Arthur Simone, Jr., M.D., Ph.D.

Project Manager: Lisa Milandro

Keywords: clinical studies, multi-center, combination drug, crossover design, generalizability, quality of life, standard of evidence, active control/non-inferiority, pooling

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1. Executive Summary of Statistical Findings

1.1 Conclusions and Recommendations

The evidence submitted does not persuasively support the efficacy of Lidopel for [redacted]. The global reason is the presence of only a single favorable study (99-07.0), from among the five randomized studies submitted, for the 20mA-minutes dose.

Substantiation of findings
The quality and quantity of evidence do not meet the standard of evidence needed to demonstrate effectiveness as discussed in an FDA guidance document[1]. Only one dose (20mA-min) of the many studied seemed to demonstrate some efficacy; this was seen in only one study (99-07.0) of the three that investigated 20mA-minutes.

The effect seen in Study 99-07.0 for the 20mA-minute dose was not supported by evidence from the other studies. Of the five randomized studies submitted, Study 99-07.0 was the only study to support the efficacy of Lidopel.

Under certain circumstances, a single positive study may be sufficient, especially in settings where a placebo-controlled study cannot be repeated. An example would be a product that demonstrated a survival advantage over placebo. In these cases the study is generally a multicenter study.

Page 12 of the guidance document[1] states such studies "are typically multicentered with clear prospectively determined clinical and statistical analytic criteria. These studies are less vulnerable to certain biases, are often more generalizable, may achieve very convincing statistical results, and can often be evaluated for internal consistency across subgroups, centers, and multiple endpoints"

In this case, Study 99-07.0 was not a multicenter study. In the absence of a randomized, multicenter study, a randomized study conducted at one site only must provide solid evidence of efficacy based on well-designed and conducted studies. Study 99-07.0 does not meet these criteria.

As a stand-alone study, 99-07.0 is relatively small. Only 60 subjects were enrolled at the 20mA-minute dose. Moreover, the results from this "single center may be dependent on site or investigator specific factors .... In such cases, the results, although correct, may not be generalizable to the intended population[1]."

Because the one study (99-07.0) that showed a statistically significant effect was a single center study, relatively few subjects received 20mA-minute and the results were not independently substantiated, generalizing the results to the general population does not seem appropriate.

Further development of this product needs to include a multicenter, randomized, controlled study.

[1] See "Guidance for industry: Providing clinical evidence of effectiveness for human drugs and biological products"; HHS/FDA/CDER and HHS/FDA/CBER; May 1998. Can be located on the internet at: http://www.fda.gov/cder/guidance/1397fnl.pdf.

Non-inferiority with Iontocaine

Non-inferiority with Iontocaine cannot be concluded based on the results from Study 001-1-03.0. The patch size and dose used for Iontocaine are not currently approved. The 20mA-minute dose is half the currently approved dose of 40mA-minute and the patch size (10.1 cm^2) is larger than the currently approved size.

Iontocaine as used in this study, therefore, may be less effective than the currently approved product. Any and its implication for efficacy of Lidopel must be interpreted carefully.

The patch size (10.1 cm^2) studied is larger than th (8.1 cm^2) It is also larger than the size used (8.1 cm^2) in Study 99-07.0, whose results justified the selection of the 20mA-minute dose for the non-inferiority study.

Visual Analogue Scales

The Visual Analogue Scales *as used in these studies* are problematic,

Insufficient evidence was submitted to establish the validity and reliability of the scales used in the studies. The information submitted to support the use of the VAS instruments addressed the use of these instruments for conditions with chronic pain, where the goal is to reduce pain and suffering. The use of VAS instruments in pain-free individuals undergoing venipuncture, for example, was not addressed.

The format of the VAS instruments was not identical to the literature cited by the applicant to support the validity and reliability of the instruments. Instead, the anchors are reversed from what was described.

Insufficient information was submitted to explain the implementation of the VAS in the adult studies. Due to the lack of this information, we can not establish whether standardized instructions and procedures were used.

Standardized instructions and procedures were not included in the submission. A site inspection of the tudy confirmed the absence of standardized instructions for

Choice of placebo

The placebo in these studies contained epinephrine. The volume of epinephrine contained in placebo was greater than the volume contained in Lidopel. The amount of epinephrine delivered by iontophoresis, therefore, increased with increasing doses and the amount delivered was greater than the amount delivered by

Lidopel.

The results from Study 99-07.0, in which Lidopel differed significantly from placebo at 20mA-minutes, suggested a dose response among placebo-treated subjects. Possibly, if a "true" placebo had been used, differences could have been detected at the higher doses.

1.2 Brief Overview of Clinical Studies

Each of the five randomized controlled studies reported in the submission was conducted at a single study site. A current of 4 mA was common to all studies. Across the studies, the duration of treatment ranged from 5 minutes to 20 minutes, corresponding to total doses ranging from 20 mA·minutes to 80 mA·minutes. The size of the electrodes ranged from 8.1 cm^2 to [redacted] cm^2.

[redacted] The other studies enrolled healthy volunteers to assess the effect of Lidopel on subjects undergoing venipuncture or punch biopsy. Subjects with skin lesions were used to assess the effect for subjects undergoing shave removal. Although the anesthetic effect of Lidopel was assessed for all subjects, the assessment of the analgesic effect was limited to those subjects who had a successful anesthetic effect.

2. Introduction

The cover letter to the September 26, 2003 submission states the applicant (see page 3 of Volume 1, submitted 9/26/03):

> ...is requesting approval for Lidopel as "indicated for [redacted]

For subjects undergoing punch biopsy or shave removal, visual analogue scales (VAS) were used to assess the analgesic effect only for those subjects who experienced adequate anesthesia as determined by a pin-prick test.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

Only three of the five randomized, controlled studies are reviewed here. Two were not reviewed because insufficient numbers of placebo-treated subjects were evaluated for adequacy of analgesia. Moreover, all subjects who were evaluated needed to have passed a pin-prick test, resulting in a highly selected group available for evaluation.

Study 97-07-0 (Anesthetic effect of Lidopel HCl and epinephrine administered via iontophoresis to subjects undergoing superficial dermatologic procedures) evaluated the analgesic effect for only 14 of 48 enrolled subjects. All 14 received Lidopel.

Similarly, only 2 of 20 placebo-treated subjects versus 49 of 60 Lidopel-treated subjects were evaluated for adequacy of analgesia in Phase 1 of Study 99-02.0 (Anesthetic effect of 2% Lidocaine HCl and epinephrine 1:100,000 delivered via the Dupel Iontophoresis System to subjects undergoing shave removals). In Phase 2, 35 of 40 Lidopel-treated subjects and 5 of 20 placebo-treated subjects were evaluated.

3.1.1 Visual analog scales

Reliability and validity of the VAS as used in the studies

Design of VAS instrument
The applicant states the anchors for the VAS are identical to that "described and validated by Huskinsson"[2]. Although this statement is accurate, it does not tell the complete story. The studies used a horizontal layout for the 100mm VAS. The *left anchor was labeled "No pain"* and the *right anchor was labeled "Pain as bad as it could be".* Above the horizontal scale appeared the wording:

> Please rate any degree of discomfort experienced during the blood draw procedure by placing a mark on the line below.

The placement of the anchors, however, differs from the examples shown in McDowell and Newell[2]. The examples show the left anchor as "PAIN AS BAD AS IT COULD BE" and the right anchor is "NO PAIN". The example use all capital letters for the anchors.

Although these format issues may appear trivial, they are important to the proper development and validation of an instrument. Not only must an instrument be validated in the population to be studied, the validation must use the exact format that will be used in the studies.

Type of pain measured
The VAS instruments cited in the literature submitted by the applicant were designed to measure pain relief over time among subjects with rheumatic diseases and other chronic conditions. None of the information describes the use of VAS in the experimental setting of inflicting pain where none existed. Huskisson (1974)[3] notes "measurement of pain in disease should not be confused with measurement of experimental pain" (this article was cited by the applicant to support the validity and reliability of the VAS).

Format of the form used to capture pain information and satisfaction with treatment
The form used to capture the pain information contained two scales. One was the "100mm Visual Analog Scale (VAS)" and below it was the "Eleven-point Categorical Scale" for satisfaction with treatment.

The VAS is described above. The satisfaction scale was also a horizontal layout with the left anchor labeled "Not at all satisfied" and the right anchor labeled "Completely satisfied". Unlike the VAS, this scale contained tick marks in increments of one, starting at 0 and ending at 10. Above the scale appeared the wording:

> Please rate your overall satisfaction with the iontophoretic treatment and blood draw

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[2] I McDowell and C Newell. Measuring Health: A Guide To Rating Scales and Questionnaires, Oxford University Press, New York, 1987.

[3] EC Huskisson. "Measurement of pain", *Lancet*, 2:1127-1130, 1974.

procedure below by circling one of the numbers.

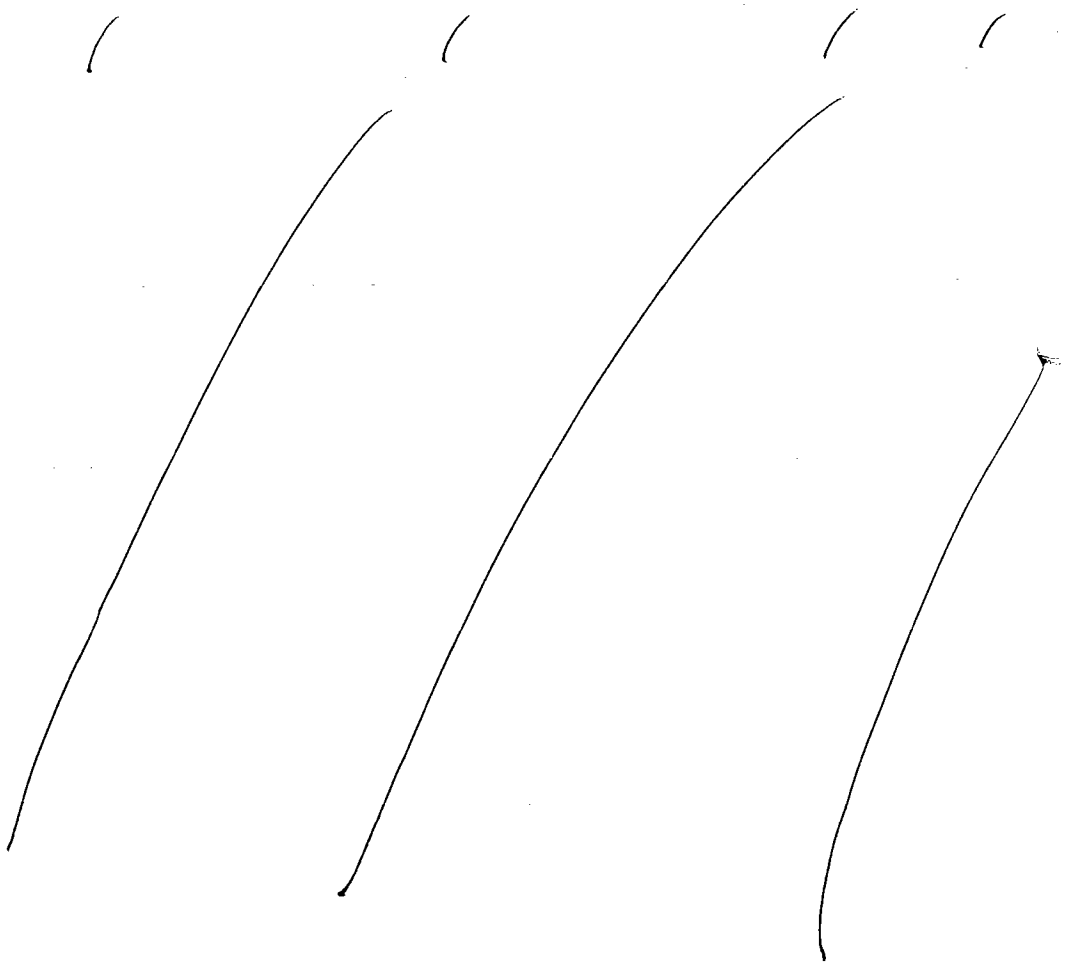
The *horizontal layout* of the VAS without intervening tick marks between the anchors is typical for studies using a VAS. What differs, however, is the *presence of a 2nd scale on the same capture form.* Although appropriate for a categorical scale, the tick marks on the scale may have influenced the results recorded for the VAS.

Information on the validation of the form containing both the VAS and the categorical scale was not provided. A better design would use a separate form for each scale.

Administration of the VAS to subjects

The method of implementation for the VAS depended on the requirements of each study; see submissions dated 5/21/2004 and 6/30/2004. These submissions, however, do not provide the information needed for us to evaluate the procedures used by study personnel. Instead, the submissions cite the study protocols, each of which uses the following phrase: "subjects will be asked to rate any discomfort experienced [procedure description; venipuncture for example] on a 100 mm visual analog scale (VAS) for pain intensity."

Details on how the subjects were asked to rate information is important to determining whether subjects were asked in exactly the same manner. We can not be sure this was the case.



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3.1.2 Size of electrodes

The size of the electrodes varied across studies (Table 3.1), which complicates the interpretation of study results. For a given dose, a larger electrode delivers the dose over a larger area than does a smaller electrode. The result is less penetration with the larger electrode.

The difference in electrode sizes is particularly important to the interpretation of Study 00-1-03.0 (non-inferiority), relative to the other studies. The choice of a 20 mA-minute dose for this study was based on the results from Study 99-07.0. The electrode sizes, however, are different: 10.1 cm^2 for 00-1-03.0 versus 8.1 cm^2 for 99-07-0.

Table 3.1. Sizes of electrodes used in the studies, by procedure. A 4 mA current was used in all studies.

Study	Procedure	Dose (mA-min)	Electrode size
97-07.0	Punch biopsy	80	8.1 cm^2
		80	— cm^2:
97-07.0	Shave removal	40	→ . cm^2:
99-02.0	Shave removal	80	8.1 cm^2
		60	8.1 cm^2
		40	8.1 cm^2
99-07-0	Venipuncture	40	8.1 cm^2
		30	8.1 cm^2
		20	8.1 cm^2
99.14.0	Venipuncture	40	8.1 cm^2
		20	8.1 cm^2
00-1-03.0	Venipuncture	20	10.1 cm^2

3.1.3 Choice of Placebo

The placebo in these studies contained epinephrine. Instead of containing a volume of epinephrine equal to the epinephrine volume in Lidopel, the volume in placebo was greater than that in Lidopel. The amount of epinephrine delivered by iontophoresis increased with increasing doses and the amount delivered was greater than the amount delivered by Lidopel. The results from Study 99-07.0, in which Lidopel differed significantly from placebo at 20mA-minutes, suggested a dose response among placebo-treated subjects. Possibly, if a "true" placebo had been used, differences could have been detected at the higher doses.

3.1.4 Study 99-07.0: Anesthetic Effect of 2% Lidocaine HCl and Epinephrine 1:100,000 Delivered via the Dupel Iontophoresis System to Subjects Undergoing Venipuncture

Design

This was a single center, double-blind, placebo-controlled, randomized study of healthy volunteers undergoing venipuncture. In *Phase 1* of the study, a total of 60 volunteer subjects were randomized in an equal allocation to three dosage levels: 20mA-minute, 30mA-minute and 40mA-minute. The lowest dose (20mA-minute) was selected for use in Phase 2. *Phase 2* enrolled a total of 40 additional subjects, all of whom received 20mA-minute during this phase. The electrode size was 8.1 cm^2.

Each subject was treated simultaneously with Lidopel on one arm and Placebo on the other. Treatments were randomly assigned to each arm. During the study the drugs were identified as Drug A and Drug B. (Drug A was placebo and Drug B was active treatment.) After iontophoresis treatment, 5 cc of blood was withdrawn from each subject's arms. The first blood draw was randomly assigned to one of the two arms.

Subjects were asked to rate any discomfort experienced during the blood draws on a 100 mm visual analog scale.

The study report presents the results of the combined study population of the 60 subjects receiving the selected dose (20mA-minute). A Wilcoxon Signed Rank test compared the VAS between the right and left arms.

Efficacy Results

Applicant's

Based on a comparison of data combined across all Lidopel doses versus data combined across all Placebo doses, the applicant concluded the Phase 1 results indicated an acceptable anesthetic effect was achieved based on a statistically significant difference in pain ratings between Lidopel and Placebo. Comparisons between treatments within doses were not statistically significant. Due to the lack of a dose-response finding in Phase 1, Phase 2 used the lowest dose (20mA-minute).

The data for the 20mA-minute doses were combined from both phases for analysis. The justification for this pooling was the lack of statistical significance between phases for subject factors (demographic characteristics, skin type and skin complexion) and for patient outcomes (VAS and satisfaction scores).

The applicant concluded active treatment (20mA-minute) was significantly better than placebo, based on the results from the VAS assessments for the 60 subjects who received 20mA-minute in either Phase 1 or Phase 2 ($p<0.001$, Wilcoxon Signed Rank Test).

Statistical Reviewer's – Phase 1

The applicant's analyses of the Phase 1 data did not properly reflect the study design. The analyses did not adjust for the randomization of treatment to arm or for the randomization of the first blood draw to one of the arms. Instead, the applicant performed a sequence of tests, each of which ignored study design features. First, the applicant compared the VAS between blood draws (first versus second) and concluded the difference was not statistically significant. Next they compared the VAS scores between Lidopel and Placebo. This difference was statistically significant. Then the VAS scores were compared within each treatment group. None of these comparisons was statistically significant, nor did the applicant "observe" a trend.

The analyses of the Phase 1 data need to consider the following study design features, which include three randomizations per subject (Table 3.2):

- Each subject was randomized to *one of three treatment groups*:
  20mA-min
  40mA-min
  60mA-min
- Each subject was randomized to *one of two sequences*:
  Placebo (left arm) and Lidopel (right arm)
  Lidopel (left arm) and Placebo (right arm)

- The first blood draw was randomized to *one of the two arms*:
  Left Arm followed by Right Arm
  Right Arm followed by Left Arm
- Subjects served as their own controls

Table 3.2. Study 99-07.0: Allocation of study subjects in Phase 1. First randomization: 20 subjects were randomized to each treatment. Second randomization: within each treatment, Placebo was randomly assigned to the left arm of 10 subjects; Lidopel was randomized to the left arm of the other 10 subjects. Third randomization: within each of these sequences, the first blood draw was randomized to the left arm followed by the right arm for half the subjects and to the right arm followed by left arm for the other half.

		First Blood Draw (3rd randomization)	
Treatment (1st randomization)	Sequence (randomized to left arm) (2nd randomization)	Right Arm (# subjects)	Left Arm (# subjects)
20mA-min	Placebo (left arm), Lidopel (right arm)	5	5
	Lidopel (left arm), Placebo (right arm)	5	5
40mA-min	Placebo (left arm), Lidopel (right arm)	5	5
	Lidopel (left arm), Placebo (right arm)	5	5
60mA-min	Placebo (left arm), Lidopel (right arm)	5	5
	Lidopel (left arm), Placebo (right arm)	5	5

Using data from Phase 1 only, I fit a linear model with the following terms:

Dependent variable:
  VAS score
Main effects:
  Dose (20mA-minute, 30mA-minute or 40mA-minute)
  Treatment (Lidopel or Placebo)
  Sequence (Lidopel [left arm] and Placebo [right arm]; or Lidopel [right arm] and Placebo [left arm])
  Arm (Right arm receives 1st blood draw or Left arm receives 1st blood draw)
Interaction terms:
  Dose*Treatment
  Subject*Dose*Sequence

While the results indicate the reduction in VAS for Lidopel-treated subjects was significantly greater than the reduction in VAS for Placebo-treated subjects (p=0.0002[7]; Table 3.3), the effect appears to be driven by the difference observed at 20mA-minute (Table 3.4).

[7] This was tested by comparing the treatment difference (Lidopel-Placebo) across the three doses, using the main effect for treatment and the interaction between dose and treatment.

Table 3.3 Study 99-07.0, Phase 1: Results of Analysis of Variance for VAS

Term in linear model	Degrees of Freedom	F -value	p-value
Dose	2	.96	.3878
Treatment	1	15.48	.0002
Dose x Treatment	2	2.63	.0806
Sequence	1	2.88	.0954
Arm	1	1.78	.1873
Subject x Sequence x Dose	56	2.02	.0048

Table 3.4. Study 99-07.0, Phase 1: Estimated difference of VAS between Lidopel and Placebo, by Dose

Dose	Estimated difference (VAS for Lidopel) – (VAS for Placebo)	Standard Error	p-value	95% confidence interval
20mA-min	-17.1	4.2	.0001	-25.4, -8.8
30mA-min	-4.7	4.2	.2625	-13.0, 3.6
40mA-min	-6.4	4.2	.1260	-14.7, 1.9

A test for linear trend in the treatment effect was not statistically significant at α=0.05 (p=.074). The treatment effect at 20mA-min was statistically significant (p=0.0001), and was greater than the effects at the other two doses.

The reduction in VAS for the Placebo-treated subjects increased with increasing doses (p= 0.03, test for linear trend).

Table 3.5. Study 99-07.0, Phase 1: Least squares means (LSMEAN) of VAS for Placebo, by dose

Dose	Estimate for Placebo (LSMEAN)	Standard Error	p-value	95% confidence interval
20mA-min	23.1	4.2	.0001	14.9, 31.4
30mA-min	16.0	4.2	.2625	7.7, 243
40mA-min	13.8	4.2	.1260	5.5, 22.1

Table 3.6. Study 99-07.0, Phase 1: Differences between doses among Placebo-treated subjects

Dose Comparison	Estimated difference between doses	Standard Error	p-value	95% confidence interval
30mA-min versus 20mA-min	-7.15	4.2	.0906	-15.4, 1.1
40mA-min versus 20mA-min	-9.25	4.2	.0299	-17.5, -1.0
40mA-min versus 30mA-min	-2.10	4.2	.6150	-10.4, 6.2

Statistical Reviewer's – Phase 2

In Phase 2, 40 subjects were randomized in a 1:1 ratio to one of two treatment sequences (Table 3.7):

- Lidopel applied to left arm and Placebo applied to right arm
- Lidopel applied to right arm and Placebo applied to left arm.

Following this randomization, the first blood draw was randomly assigned to either the right arm or left arm.

The only dose studied was 20mA-minute.

Table 3.7. Study 99-07.0, Phase 2: Overview of study design for Phase 2

Treatment	Sequence (randomized to left arm)	First Draw: Right Arm (# subjects)	First Draw: Left Arm (# subjects)
20mA-min	Placebo (left arm), Lidopel (right arm)	10	10
	Lidopel (left arm), Placebo (right arm)	10	10

I fit a linear model with the following terms:

Dependent variable:
VAS score
Main effects:
Treatment (Lidopel or Placebo)
Sequence (Lidopel [left arm] and Placebo [right arm]; or Lidopel [right arm] and Placebo [left arm])
Arm (Right arm receives 1st blood draw or Left arm receives 1st blood draw)

The VAS scores for Lidopel treatment were significantly lower than those for Placebo (p=0.012).

Statistical Reviewer's – Phase 1 and Phase 2

Phase 1 included three doses. By contrast Phase 2 studied a single dose only (20mA-minute). The selection of 20mA-minute for Phase 2 was based on the results from Phase 1.

Using data from subjects who were treated with 20mA-min in either Phase 1 or Phase 2, I fit a linear model with the following terms:

Dependent variable:
VAS score
Main effects:
Treatment (Lidopel or Placebo)
Phase (Phase 1 or Phase 2)
Sequence (Lidopel [left arm] and Placebo [right arm];
or Lidopel [right arm] and Placebo [left arm])
Arm (Right arm receives 1st blood draw or Left arm receives 1st blood draw)
Interaction terms:
Treatment*Phase
Subject*Phase*Sequence

The difference between Lidopel and Placebo was statistically significant; see Table 3.8.

Table 3.8. Study 99-07.0, Phases 1 and 2: Results of Analysis of Variance for VAS

Term in linear model	Degrees of Freedom	F Value	p-value
Treatment	1	16.94	.0001
Treatment x Phase	1	.76	.3865
Phase	1	.27	.6055
Sequence	1	1.29	.2614
Arm	1	0	.9551
Subject x Sequence x Phase	57	1.37	.1201

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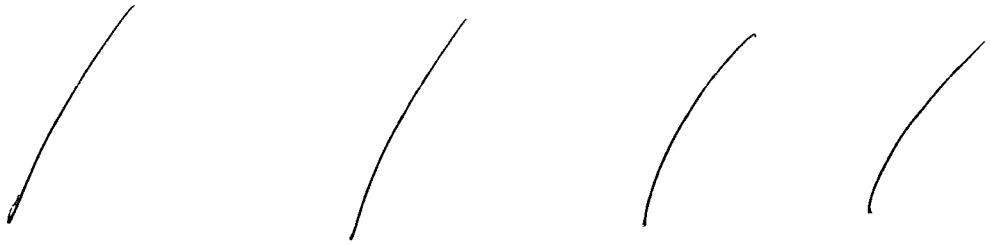

3.1.6 Study 001-03.0: Comparative Study of Two Iontoophoretically Delivered 2% Lidocaine HCl and Epinephrine 1:100,000 Formulations in Subjects Undergoing Venipuncture

Design

This was a single center, randomized, active-controlled, crossover study. Subjects received Active treatment and Placebo treatment simultaneously at each visit; both arms were used. The study objective was to demonstrate a dose of Empi's 2% Lidocaine HCl and Epinephrine 1:100,000 delivered via the Empi Dupel produced an equivalent anesthetic effect to that of Iontocaine administered via the Iomed Phoresor in subjects undergoing a venipuncture procedure. A dose of 20mA-min was chosen based on the results from Phase 1 and Phase 2 of Study 99-07.0.

Thirty subjects were randomized to one of two sequences. Treatment visits (sessions) were separated by a 7 to 14 day washout period.

- Sequence A (active treatment);
  - 1st visit: Empi Dupel
  - 2nd visit: Iomed system

- Sequence B (active treatment)
  - 1st visit: Iomed system
  - 2nd visit: Empi Dupel

At each treatment, iontophoresis treatment was simultaneously applied to both the left and right arms, with one arm receiving the active drug and the other arm receiving the placebo drug. The choice of arm to receive the active treatment was randomly assigned and remained the same at the two treatment visits. The right arm was used for the first blood draw at each visit.

Efficacy Results

Applicant

The applicant concludes

> "The lower end of the 95% confidence interval of the mean within-subject difference between the VAS reduction observed for the Empi Dupel and Iomed Phoresor devices was within the critical difference of 10 points specified in the study protocol for demonstrating equivalence."

Statistical Reviewer's

The non-inferiority comparison with Iontocaine may not be a fair comparison. Lidopel may be comparing itself with an ineffective dose and delivery system. Not only is the 20mA-minute half the currently approved dose of 40mA-minute, the patch size is larger than what is currently approved for the Iomed system. To claim "non-inferiority" against what may be an ineffective product is similar to claiming "non-inferiority" with

placebo.

Other issues affect the interpretation of the study results for the to-be-marketed product. For instance, the size of the electrode is larger than the electrode in the to-be-marketed product. The size of the electrode used in this study is larger than that used for Study 99-07.0, whose results were the basis for the dose used in this study.

3.2 Evaluation of Safety

See Dr. Simone's review.

4. Summary and Conclusions

4.1 Statistical Issues and Collective Evidence

The evidence submitted does not persuasively support the efficacy of Lidopel for

Of the five randomized, controlled studies, only one appeared favorable (99-07.0). It supported efficacy for the 20mA-minutes dose.

4.2 Conclusions and Recommendations

The evidence submitted does not persuasively support the efficacy of Lidopel for

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Lisa A. Kammerman
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