

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-114**

**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 CLINICAL STUDIES

**NDA/Serial Number:** NDA 22-114  
**Drug Name:** Sterile LHM (lidocaine hydrochloride monohydrate) Product  
**Indication(s):** Local analgesia prior to venipuncture or cannulation  
**Applicant:** Anesiva, Inc.  
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**Review Priority:** Standard  
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## Table of Contents

|  |           |
|--|-----------|
| <b>1. EXECUTIVE SUMMARY</b> .....                        | <b>4</b>  |
| 1.1 CONCLUSIONS AND RECOMMENDATIONS .....                | 4         |
| 1.2 BRIEF OVERVIEW OF CLINICAL STUDIES .....             | 4         |
| 1.3 STATISTICAL ISSUES AND FINDINGS .....                | 5         |
| <b>2. INTRODUCTION</b> .....                             | <b>5</b>  |
| 2.1 OVERVIEW .....                                       | 5         |
| 2.2 DATA SOURCES .....                                   | 6         |
| <b>3. STATISTICAL EVALUATION</b> .....                   | <b>6</b>  |
| 3.1 EVALUATION OF EFFICACY .....                         | 6         |
| 3.2 EVALUATION OF SAFETY .....                           | 15        |
| <b>4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS</b> ..... | <b>16</b> |
| <b>5. SUMMARY AND CONCLUSIONS</b> .....                  | <b>16</b> |
| 5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE .....     | 16        |
| 5.2 CONCLUSIONS AND RECOMMENDATIONS .....                | 17        |
| 5.3 REVIEW OF CLINICAL STUDIES OF PROPOSED LABEL .....   | 17        |
| <b>APPENDIX</b> .....                                    | <b>19</b> |
| <b>SIGNATURES/DISTRIBUTION LIST</b> .....                | <b>27</b> |

## LIST OF TABLES

|   |    |
|---|----|
| Table 1 Subject Disposition.....  | 7  |
| Table 2 Applicant’s Primary Efficacy Analysis: Study 003 FAS.....   | 10 |
| Table 3 Applicant’s Sensitivity Analysis: Study 003 ITT (Worst Possible Score Imputation).....                    | 11 |
| Table 4 Secondary Efficacy Analysis of Pain VAS: Study 003 FAS.....   | 11 |
| Table 5 Secondary Efficacy Analysis of Response Rate: Study 003 FAS.....  | 12 |
| Table 6 Frequency Distribution of Primary Efficacy Outcome: Study 003 FAS.....                                    | 12 |
| Table 7 Applicant’s Primary Efficacy Analysis: Study 004 FAS.....   | 13 |
| Table 8 Applicant’s Sensitivity Analysis: Study 004 ITT (Worst Possible Score Imputation).....                    | 14 |
| Table 9 Secondary Efficacy Analysis of Pain VAS: Study 004 FAS.....   | 14 |
| Table 10 Secondary Efficacy Analysis of Response Rate: Study 004 FAS.....   | 15 |
| Table 11 Frequency Distribution of Primary Efficacy Outcome: Study 004 FAS.....                                   | 15 |
| Table 12 Patient Demographic Characteristics (ITT Population).....  | 19 |
| Table 13 Reviewer’s Sensitivity Analysis: Study 003 FAS Full Effects Model (SAP Full Model).....                  | 20 |
| Table 14 Reviewer’s Sensitivity Analysis: Study 003 FAS (SAP Reduced Model).....                                  | 21 |
| Table 15 Reviewer’s Sensitivity Analysis: Study 003 FAS Main Effects Model.....                                   | 21 |
| Table 16 Reviewer’s Sensitivity Analysis: Study 003 FAS Selected Effects Model.....                               | 22 |
| Table 17 Reviewer’s Sensitivity Analysis: Study 003 ITT (Worst Possible Score Imputation) Main Effects Model..... | 22 |
| Table 18 Reviewer’s Sensitivity Analysis: Study 004 FAS Full Effects Model (SAP Full Model).....                  | 23 |
| Table 19 Reviewer’s Sensitivity Analysis: Study 004 FAS (SAP Reduced Model).....                                  | 24 |
| Table 20 Reviewer’s Sensitivity Analysis: Study 004 FAS Main Effects Model.....                                   | 24 |
| Table 21 Reviewer’s Sensitivity Analysis: Study 004 FAS Selected Effects Model.....                               | 25 |
| Table 22 Reviewer’s Sensitivity Analysis: Study 004 ITT (Worst Possible Score Imputation) Main Effects Model..... | 25 |

## LIST OF FIGURES

|   |    |
|---|----|
| Figure 1 Schematic of Study Design..... | 26 |
|---|----|

## **1. EXECUTIVE SUMMARY**

### **1.1 Conclusions and Recommendations**

Study 3268-3-003-1 and Study 3268-3-004-1 were conducted in pediatric patients, from 3 to 18 years of age, undergoing venipuncture or peripheral venous cannulation. The studies both demonstrated a greater analgesic effect of the sterile lidocaine hydrochloride monohydrate (LHM) product compared to placebo. The analgesic effect was measured on the Wong-Baker FACES pain rating scale. The effect was evident in both the applicant's analyses and the additional analyses conducted by me. Study 3268-3-003-1 also demonstrated statistically significant differences in several secondary efficacy outcomes including the 100 mm visual analog scale (VAS) pain scores measured in patients aged 8 to 18 and the responder rate between the LHM product and placebo. However, Study 3268-3-004-1 did not demonstrate statistically significant differences in the 100 mm VAS pain scores measured in patients aged 8 to 18 or the responder rate between the LHM product and placebo. Moreover, the analgesic effect of the LHM product was not demonstrated in some of my additional analyses for Study 3268-3-004.

Based on my evaluation of the collective evidence, I conclude that the two studies were successful in demonstrating superiority of the LHM product over placebo.

### **1.2 Brief Overview of Clinical Studies**

The applicant submitted the results and data from five efficacy studies, 3268-3-003-1, 3268-3-004-1, 3268-4-400-2, 3268-4-401, and 3268-2-002-1. Two studies, 3268-3-003-1 and 3268-3-004-1, investigated the to-be-marketed version of ND5.3A device (0.5 mg lidocaine/21 bar of helium pressure) and were considered as confirmatory trials. The three latter studies investigated the ND5.3 device (0.5 mg lidocaine/20 bar of helium pressure) and were considered as supportive trials with the ND5.3 device (0.5 mg lidocaine/20 bar of helium pressure). My review focused on the two confirmatory studies with the ND5.3A device.

Studies 3268-3-003-1 and 3268-3-004-1 (referred to as Study 003 and Study 004 throughout my review) were double-blind, placebo-controlled, multi-center trials investigating the safety and analgesic effect of the LHM product in pediatric patients (from 3 and 18 years of age inclusive) undergoing venipuncture or peripheral venous cannulation. In Study 003, 579 patients were randomized to a single dose of the LHM product (n = 292) or placebo (n = 287) in a 1:1 ratio. The primary efficacy outcome was pain assessed via the Wong-Baker FACES pain rating scale. Secondary efficacy measures included a 100 mm VAS pain score (patients aged 8 to 18) and the responder rate (responders defined by having a 0 or 1 on the FACES scale).

### **1.3 Statistical Issues and Findings**

During the review process, the review team questioned whether the statistical analysis plan had been finalized prior to the database-lock. I requested the applicant send information on the sign-off dates for the final protocol, the final SAP, and the database-lock. The concern was resolved after the applicant sent necessary documents for the official sign-off dates which indicated a proper order for the protocol finalization, the SAP finalization, and the database-lock.

Also, the clinical reviewer was concerned that the instructions utilized for the pain rating were not the standard instructions used for the Wong-Baker FACES. The review team consulted the Study Endpoints and Label Development Team and the issue was resolved.

The primary efficacy outcome was analyzed using an analysis of variance model with terms for treatment, age group, and treatment-by-age group interaction. When the applicant's primary analysis model is applied to both studies, it demonstrates a significant difference between LHM and placebo. In my opinion, there was some ambiguity regarding the factors to be included in the model; therefore, I also conducted several additional analyses including various factors in the model. My additional analyses for Study 003 yielded results and conclusions that were consistent with the applicant's results and conclusions. However, some of my additional analyses for Study 004 did not yield the same results and conclusions as those of the applicant. Since my additional analyses can be considered exploratory and the results of the applicant's primary analyses were consistent, I was not concerned with the inconsistent results of my additional analyses.

The applicant used a worst possible score ("5" for missing Wong-Baker pain rating scale and "100" for 100 mm VAS pain score) imputation strategy in the ITT analysis. Since the dropout rate was low and the worst possible score imputation strategy was used, missing data was not an issue.

Patients whose procedures were not successful on the first attempt were replaced. According to the clinical review team, treatment is considered to be independent of a success or failure of a procedure; therefore in my opinion, the inclusion of the replacement patients was not overly concerning.

## **2. INTRODUCTION**

### **2.1 Overview**

#### **2.1.1 Drug class and regulatory history**

The applicant described the sterile LHM product in the submission as follows:

The Sterile LHM Product (previously referred to as ALGRX 3268) is a needle-free, single-use, disposable product that delivers local anesthetic, Lidocaine hydrochloride monohydrate (LHM), into the epidermis to reduce or eliminate the pain associated with venipuncture or cannulation procedures. The product uses pressurized helium to accelerate drug particles to velocities sufficient to penetrate into the epidermis. The pressure of the Sterile LHM Product and matching sham placebo was established as 21.0 bar  $\pm$  1.0 bar (20 – 22 bar). Administered LHM has a rapid onset of action, within one to three minutes.

The proposed trade name is Zingo®. The applicant introduced the sterile LHM product to the agency via IND 54,740 on 10 December 1997. 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, amended protocols were submitted in January of 2005.

### **2.1.2 Proposed Indication for the sterile LHM Product**

The proposed indication for the sterile LHM product is for use on intact skin to provide local analgesia prior to venipuncture and intravenous cannulation.

### **2.2 Data Sources**

NDA 22-114 was submitted on November 21, 2006 and can be found in the electronic document room (EDR) of the Center for Drug Evaluation and Research. The electronic SAS data sets were also provided in the EDR using the following path:

\\CDSUB1\evsprod\NDA22114\0000

## **3. STATISTICAL EVALUATION**

### **3.1 Evaluation of Efficacy**

#### **3.1.1 Study Design and Endpoints**

Studies 003 and 004 were multi-center, double-blind, placebo-controlled, parallel-group, single-dose trials of the safety and efficacy of the sterile LHM product compared to placebo in pediatric patients undergoing venipuncture or peripheral venous cannulation at the antecubital fossa (ACF) and back of hand (BOH). In Study 003, 579 eligible patients were randomized to the sterile LHM product or placebo in a 1:1 ratio at six centers within

the United States. In Study 004, 535 eligible patients were randomized to the sterile LHM product or placebo in a 1:1 ratio at nine centers within the United States. Randomization at each clinical site was stratified by age group (3 to 7 years, 8 to 12 years and 13 to 18 years). Figure 1 in the appendix presents a schematic of the study design.

The primary efficacy endpoint was the child’s assessment of pain on venipuncture or peripheral venous cannulation performed 1-3 minutes after LHM or placebo administration measured using the Wong-Baker FACES pain rating scale anchored at 0 for “No Hurt” and 5 for “Hurts Worst”.

The secondary efficacy variables included the following:

- Assessment of pain on a 100 mm VAS pain score anchored at 0 for “No Pain” and 100 for “Worst Possible Pain” measured only for children of ages between 8 and 18 inclusive
- Responder rate (responder if Wong-Baker FACES pain score is equal to 0 or 1)
- Parent’s/legal guardian’s assessment of their child’s pain using a 100 mm VAS pain score (0 for “No Pain” and 100 for “Worst Possible Pain”).

### 3.1.2 Patient Disposition and Demographics

Table 1 summarizes the patient disposition. Less than 5% of the patients discontinued from both studies 003 and 004. With the exception of one patient, all dropouts occurred because of failed venipuncture or cannulation procedures.

**Table 1 Subject Disposition**

|                         | Number (%) of Patients |          |          |
|-------------------------|------------------------|----------|----------|
|                         | LHM                    | PLACEBO  | Total    |
| <b>Study 003</b>        |                        |          |          |
| Patients treated (ITT)* | 292                    | 287      | 579      |
| Ages 3-7 yrs.           | 86 (30)                | 87 (30)  | 173 (30) |
| Ages 8-12 yrs.          | 94 (32)                | 98 (34)  | 192 (33) |
| Ages 13-18 yrs.         | 112 (38)               | 102 (36) | 214 (37) |
| FAS†                    | 289 (99)               | 285 (99) | 574 (99) |
| Completed Study         | 278 (95)               | 276 (96) | 554 (96) |
| Discontinued Study      | 14 (5)                 | 11 (4)   | 25 (4)   |

|                         |          |          |          |
|-------------------------|----------|----------|----------|
|                         |          |          |          |
| <b>Study 004</b>        |          |          |          |
| Patients treated (ITT)* | 269      | 266      | 535      |
| Ages 3-7 yrs.           | 86 (32)  | 81 (31)  | 167 (30) |
| Ages 8-12 yrs.          | 81 (30)  | 81 (31)  | 162 (33) |
| Ages 13-18 yrs.         | 102 (38) | 104 (39) | 206 (37) |
| FAS†                    | 260 (97) | 257 (97) | 517 (97) |
| Completed Study         | 257 (95) | 255 (96) | 512 (96) |
| Discontinued Study      | 12 (5)   | 11 (4)   | 23 (4)   |

\*Includes initially randomized and replacement patients.

† FAS included all randomized patients who received study medication and had a Wong-Baker FACES measurement.

Source: Table 3, Clinical Study Report, Study 003 and Table 3, Clinical Study Report, Study 004

Table 12 in the appendix shows patient demographics by treatment group. In Study 003, the ages of patients ranged from 3 to 18 with median age of 11. In the study, 83% of the patients were Caucasian, 10% were African-American, and 1% were Asian. Fifty-two percent of the population was female. In Study 004, the ages of patients ranged from 3 to 18 with median age of 11. In the study, 68% of the patients were Caucasian, 19% were African-American, and 4% were Asian. Forty-seven percent of the population was female. There were no noticeable imbalances among treatment groups with respect to the demographic variables of age, race, and weight.

### 3.1.3 Statistical Methodologies

The applicant stated in the statistical analysis plan (SAP),

The primary analysis will compare the mean pain score within the combined 3 age groups using an ANOVA model with treatment (two levels) and age group (three levels) as the two factors and terms for treatment-by-age interactions. Terms for body site, procedure and center will be included in the model as will treatment-by-center, treatment-by-body site, and treatment-by-procedure interaction. Treatment difference and 95% confidence limits will be provided. The primary contrast is the main effect of treatment across all levels of age. To determine if there are age effects, treatment by age interaction will be examined. If  $p < .10$ , treatment contrasts within each age group will be obtained using the error terms from the full analysis. In addition, to determine if the treatment effect depends on center, body site or procedure, the corresponding interaction term will be examined. If any of these is statistically significant ( $< 0.10$ ), they will be investigated to determine the reasons for the interaction and the effect, if any, on the conclusion of the primary statistical analysis.

The results presented by the applicant suggested that the full model including additional terms for body site, procedure, and center was analyzed for exploratory purposes only.

Since I perceived there to be some ambiguity regarding the purpose of the analysis of the full model, I conducted several additional analyses including various factors in the model.

A similar ANOVA model was used to analyze the 100 mm VAS pain scores. In addition, a Cochran-Mantel-Haenszel test was used to compare responder proportions between LHM and placebo stratifying by center.

Patients who failed the procedures of venipuncture or cannulation were not included in the primary analysis. These patients were replaced with new patients. The applicant stated,

If venipuncture or cannulation was not successful on the first attempt, patients were considered non-evaluable due to the confounding effects of multiple needle insertions. In an attempt to ensure that the final sample size of evaluable patients would be close to what was planned and to maintain the balance of randomization, a subject whose venous procedure was not successful on the first attempt was to be discontinued from the study and replaced with another subject. Replacement patients were assigned the same treatment as the original randomized individuals.

The primary analysis was conducted on the full analysis set (FAS) population. The FAS population was defined as all randomized patients who received study drug and had an assessment of pain measured on the Wong-Baker FACES pain rating scale. An additional analysis used the intent-to-treat (ITT) population. The ITT population was defined as all randomized patients who received study drug. Missing data were imputed using a worst possible score imputation strategy.

#### **3.1.4 Results and Conclusions**

Tables 2 – 11 present the statistical analyses conducted by the applicant and me. Additional analyses are summarized in tables found in the appendix of my review. I confirmed the applicant's analyses. The following are the results of the analyses.

In Study 003, a greater analgesic effect (as measured by the Wong-Baker FACES pain rating scale) was achieved by pediatric patients receiving the LHM product as compared to those receiving placebo. The applicant's primary and sensitivity analyses demonstrated superiority of the LHM product to placebo (Tables 2 – 3). I additionally performed analyses using several different models incorporating various factors. The results of my analyses are in the appendix and demonstrated the statistically significant difference between the LHM product and the placebo (Tables 13 – 17 in the appendix). My conclusions were consistent with those of the applicant. In my additional analysis, there did not appear to be any heterogeneity of the treatment effect across body site or procedure.

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 VAS pain scores and the responder analysis (Tables 4 – 5). A greater percentage of study participants randomized to LHM responded favorably (defined as having a FACES score of 0 or 1) to treatment compared to study participants randomized to placebo (Table 6).

**Table 2 Applicant’s Primary Efficacy Analysis: Study 003 FAS**

| <b>Wong-Baker FACES score</b>                     |                    |                        |
|---|--------------------|------------------------|
| <b>ANOVA with trt, age_grp, trt*age_grp</b>       |                    |                        |
|   | <b>LHM (N=289)</b> | <b>PLACEBO (N=285)</b> |
| <b>LS Mean (SE)</b>                               | 1.73 (0.09)        | 2.08 (0.09)            |
| <b>Diff. from PBO (SE)</b>                        | -0.34 (0.13)       |                        |
| <b>95% Confidence Interval for the Difference</b> | (-0.60, -0.09)     |                        |
| <b>p-values</b>                                   | <b>0.0072</b>      |                        |

LSMeans and p-values calculated from ANOVA model:  $Y = trt + age\_grp + trt*age\_grp$ .  
 Source: Table 9, Clinical Study Report, Study 003

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**Table 3 Applicant's Sensitivity Analysis: Study 003 ITT (Worst Possible Score Imputation)**

| <b>Wong-Baker FACES score</b><br><b>ANOVA with trt, age_grp, trt*age_grp</b> |                    |                        |
|--|--------------------|------------------------|
|  | <b>LHM (N=292)</b> | <b>PLACEBO (N=287)</b> |
| <b>LS Mean (SE)</b>  | 1.77 (0.09)        | 2.10 (0.09)            |
| <b>Diff. from PBO (SE)</b>   | -0.33 (0.13)       |                        |
| <b>95% Confidence Interval for the Difference</b>                            | (-0.58, -0.08)     |                        |
| <b>p-value</b>   | <b>0.0107</b>      |                        |

LSMeans and p-values calculated from ANOVA model:  $Y = \text{trt} + \text{age\_grp} + \text{trt}*\text{age\_grp}$ .  
Source: Table 10, Clinical Study Report, Study 003

**Table 4 Secondary Efficacy Analysis of Pain VAS: Study 003 FAS**

| <b>100 mm Pain VAS, Ages 8-18 Years</b><br><b>ANOVA with trt, age_grp, trt*age_grp</b> |                    |                        |
|--|--------------------|------------------------|
|  | <b>LHM (N=203)</b> | <b>PLACEBO (N=200)</b> |
| <b>LS Mean (SE)</b>  | 21.5 (1.8)         | 32.0 (1.8)             |
| <b>Diff. from PBO (SE)</b>   | -10.5 (2.5)        |                        |
| <b>95% Confidence Interval for the Difference</b>                                      | (-15.4, -5.56)     |                        |
| <b>p-value</b>   | <b>&lt;0.001</b>   |                        |

LSMeans and p-values calculated from ANOVA model:  $Y = \text{trt} + \text{age\_grp} + \text{trt}*\text{age\_grp}$ .  
Source: Table 11, Clinical Study Report, Study 003

**Table 5 Secondary Efficacy Analysis of Response Rate: Study 003 FAS**

| <b>Responder if 0 or 1 in Wong-Baker FACES score</b> |                    |                        |
|--|--------------------|------------------------|
|  | <b>LHM (N=289)</b> | <b>PLACEBO (N=285)</b> |
| <b>Number of Responders</b>                          | 160                | 123                    |
| <b>Responder Rate</b>                                | 55.4%              | 43.2%                  |
| <b>Odds Ratio</b>                                    | 1.65               |                        |
| <b>p-value</b>                                       | <b>0.0033</b>      |                        |

Source: Table 12, Clinical Study Report, Study 003

**Table 6 Frequency Distribution of Primary Efficacy Outcome: Study 003 FAS**

| <b>Wong-Baker FACES pain rating scale score</b> |                    |                        |
|---|--------------------|------------------------|
|   | <b>LHM (N=289)</b> | <b>PLACEBO (N=285)</b> |
| 0   | 74 (26%)           | 44 (15%)               |
| 1   | 86 (30%)           | 79 (28%)               |
| 2   | 53 (18%)           | 71 (25%)               |
| 3   | 31 (11%)           | 34 (12%)               |
| 4   | 18 (6%)            | 22 (8%)                |
| 5   | 27 (9%)            | 35 (12%)               |

In Study 004, a greater analgesic effect (as measured by the Wong-Baker FACES pain rating scale) was achieved by pediatric patients receiving the LHM product as compared to those receiving placebo. The applicant's primary and sensitivity analyses demonstrated superiority of the LHM product to placebo (Tables 7 – 8). Similar to the former study, I additionally performed analyses using several different models incorporating various factors. Although some of my analyses demonstrated a greater analgesic effect of the LHM product compared to placebo (Tables 20 – 22 in the appendix), two of the models explored did not yield statistically significant differences (Tables 18 – 19 in the appendix).

There were no statistically significant differences between treatment and placebo either in the VAS pain scores or in the responder analysis (Tables 9 – 11).

**Table 7 Applicant's Primary Efficacy Analysis: Study 004 FAS**

| <b>Wong-Baker FACES score</b>                     |                    |                        |
|---|--------------------|------------------------|
| <b>ANOVA with trt, age_grp, trt*age_grp</b>       |                    |                        |
|   | <b>LHM (N=260)</b> | <b>PLACEBO (N=257)</b> |
| <b>LS Mean (SE)</b>                               | 1.28 (0.09)        | 1.67 (0.09)            |
| <b>Diff. from PBO (SE)</b>                        | -0.38 (0.12)       |                        |
| <b>95% Confidence Interval for the Difference</b> | (-0.62, -0.14)     |                        |
| <b>p-value</b>                                    | <b>0.0022</b>      |                        |

LSMeans and p-values calculated from ANOVA model:  $Y = \text{trt} + \text{age\_grp} + \text{trt} * \text{age\_grp}$ .  
Source: Table 9, Clinical Study Report, Study 004

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**Table 8 Applicant's Sensitivity Analysis: Study 004 ITT (Worst Possible Score Imputation)**

| <b>Wong-Baker FACES score</b><br><b>ANOVA with trt, age_grp, trt*age_grp</b> |                    |                        |
|--|--------------------|------------------------|
|  | <b>LHM (N=269)</b> | <b>PLACEBO (N=266)</b> |
| <b>LS Mean (SE)</b>  | 1.38 (0.09)        | 1.77 (0.09)            |
| <b>Diff. from PBO (SE)</b>   | -0.39 (0.13)       |                        |
| <b>95% Confidence Interval for the Difference</b>                            | (-0.65, -0.13)     |                        |
| <b>p-value</b>   | <b>0.0034</b>      |                        |

LSMeans and p-values calculated from ANOVA model:  $Y = \text{trt} + \text{age\_grp} + \text{trt} * \text{age\_grp}$ .  
Source: Table 10, Clinical Study Report, Study 004

**Table 9 Secondary Efficacy Analysis of Pain VAS: Study 004 FAS**

| <b>100 mm Pain VAS, Ages 8-18 Years</b><br><b>ANOVA with trt, age_grp, trt*age_grp</b> |                    |                        |
|--|--------------------|------------------------|
|  | <b>LHM (N=180)</b> | <b>PLACEBO (N=177)</b> |
| <b>LS Mean (SE)</b>  | 15.2 (1.5)         | 18.0 (1.5)             |
| <b>Diff. from PBO (SE)</b>   | -2.8 (2.1)         |                        |
| <b>95% Confidence Interval for the Difference</b>                                      | (-7.0, 1.4)        |                        |
| <b>p-value</b>   | 0.1856             |                        |

LSMeans and p-values calculated from ANOVA model:  $Y = \text{trt} + \text{age\_grp} + \text{trt} * \text{age\_grp}$ .  
Source: Table 11, Clinical Study Report, Study 004

**Table 10 Secondary Efficacy Analysis of Response Rate: Study 004 FAS**

| Responder if 0 or 1 in Wong-Baker FACES score |             |                 |
|---|-------------|-----------------|
|   | LHM (N=260) | PLACEBO (N=257) |
| <b>Number of Responders</b>                   | 177         | 155             |
| <b>Responder Rate</b>                         | 68.1%       | 60.3%           |
| <b>Odds Ratio</b>                             | 1.44        |                 |
| <b>p-value</b>                                | 0.0540      |                 |

Source: Table 12, Clinical Study Report, Study 004

**Table 11 Frequency Distribution of Primary Efficacy Outcome: Study 004 FAS**

| Wong-Baker FACES pain rating scale score |             |                 |
|--|-------------|-----------------|
|  | LHM (N=260) | PLACEBO (N=257) |
| 0  | 92 (35%)    | 61 (24%)        |
| 1  | 85 (33%)    | 94 (37%)        |
| 2  | 42 (16%)    | 46 (18%)        |
| 3  | 18 (7%)     | 18 (7%)         |
| 4  | 7 (3%)      | 11 (4%)         |
| 5  | 16 (6%)     | 27 (10%)        |

### 3.2 Evaluation of Safety

The evaluation of safety was conducted by the clinical reviewer, Howard Josefborg, M.D.

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

The applicant explored the heterogeneity of the treatment effect across age group, 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 group ('3 - 7 yr.' vs. '8 - 12 yr.' vs. '13 - 18 yr.'), gender, or race in the Wong-Baker FACES pain rating scale. The applicant did not propose any efficacy claims for any subgroups of pediatric patients.

#### **5. SUMMARY AND CONCLUSIONS**

##### **5.1 Statistical Issues and Collective Evidence**

###### **5.1.1 Statistical Issues**

During the review process, the review team questioned whether the statistical analysis plan had been finalized prior to the database-lock. I requested the applicant send information on the sign-off dates for the final protocol, the final SAP, and the database-lock. The concern was resolved after the applicant sent necessary documents for the official sign-off dates which indicated a proper order for the protocol finalization, the SAP finalization, and the database-lock.

Also, the clinical reviewer was concerned that the instructions utilized for the pain rating were not the standard instructions used for the Wong-Baker FACES. The review team consulted the Study Endpoints and Label Development Team and the issue was resolved.

When the applicant's primary analysis model is applied to both studies, it demonstrates a significant difference between LHM and placebo. In my opinion, there was some ambiguity regarding the factors to be included in the model; therefore, I also conducted several additional analyses including various factors in the model. My additional analyses for Study 003 yielded results and conclusions that were consistent with the applicant's results and conclusions. However, some of my additional analyses for Study 004 did not yield the same results and conclusions as those of the applicant. Since my additional analyses can be considered exploratory and the results of the applicant's primary analyses were consistent, I was not concerned with the inconsistent results of my additional analyses.

The applicant used a worst possible score ("5" for missing Wong-Baker pain rating scale and "100" for 100 mm VAS pain score) imputation strategy in the ITT analysis. Since the dropout rate was low and the worst possible score imputation strategy was used, missing data was not an issue.

Patients whose procedures were not successful on the first attempt were replaced. According to the clinical review team, treatment is considered to be independent of a success or failure of a procedure; therefore, in my opinion, the inclusion of the replacement patients was not overly concerning.

### **5.1.2 Collective Evidence**

I reviewed the applicant's two efficacy studies. In reviewing the collective evidence from the applicant's analyses as well as my additional analyses, I conclude that the data provides evidence of efficacy of the LHM product.

Although Study 004 did not demonstrate statistically significant differences in the secondary efficacy variables and in some of my additional analyses, the statistically significant differences demonstrated by the primary analysis, the analysis of the main-effects model (included terms for treatment, age, center, body site, and procedure), and the analysis of the model including treatment, age group, procedure and their interactions reassured me of the efficacy of the LHM product.

### **5.2 Conclusions and Recommendations**

Studies 003 and 004 were conducted in pediatric patients undergoing venipuncture or peripheral venous cannulation. An analgesic effect (measured by the Wong-Baker FACES pain rating scale) of the LHM product was demonstrated in both studies. Specifically in Study 003, the applicant's primary analysis as well as my additional analyses yielded a statistically significant difference between the LHM product and placebo. The study also demonstrated statistically significant differences in several secondary efficacy outcomes including the 100 mm visual analog scale (VAS) pain scores and the responder rate between the LHM product and placebo. While the applicant's primary analysis showed a statistically significant difference in Study 004, the results from my some of my analyses varied depending on the factors included in the model. Moreover, the study did not demonstrate a statistically significant difference in either the 100 mm VAS pain scores or the responder rate between the LHM product and placebo.

Although Study 004 failed to demonstrate a significant difference when using alternative models or exploring some secondary outcome variables, I conclude that the collective evidence supports the efficacy of the LHM product in analgesia.

### **5.3 Review of Clinical Studies of Proposed Label**

The following is the text portion of the Clinical Study section from the proposed label.

b(4)

I found that the results are consistent with results from the reports of the integrated analyses of studies 003 and 004. However, I recommend reporting separate results for the two studies instead of the pooled results. Moreover, I do not recommend inclusion of the secondary outcomes in this label.

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APPENDIX

Table 12 Patient Demographic Characteristics (ITT Population)

Study 003:

|  | LHM<br>(n=292) | Placebo<br>(n=287) |
|--|----------------|--------------------|
| <b>Gender n (%)</b>                          |                |                    |
| Male   | 139 (47.6%)    | 137 (47.7%)        |
| Female                                       | 153 (52.4%)    | 150 (52.3%)        |
| <b>Race n (%)</b>                            |                |                    |
| Asian  | 2 (.7%)        | 5 (1.7%)           |
| Black  | 23 (7.9%)      | 35 (12.2%)         |
| Caucasian                                    | 253 (86.6%)    | 230 (80.1%)        |
| Native Hawaiian or<br>other Pacific Islander | 1 (.3%)        | 2 (.7%)            |
| Other  | 13 (4.5%)      | 15 (5.2%)          |
| <b>Age (years)</b>                           |                |                    |
| Median                                       | 11.0           | 11.0               |
| Range  | 3.0 – 18.0     | 3.0 – 18.0         |
| <b>Weight (kg)</b>                           |                |                    |
| Median                                       | 40.5           | 38.8               |
| Range  | 11.8 – 113.7   | 13.0 – 124.7       |

Study 004:

|                     | LHM<br>(n=269) | Placebo<br>(n=266) |
|---------------------|----------------|--------------------|
| <b>Gender n (%)</b> |                |                    |
| Male                | 138 (51.3%)    | 143 (53.8%)        |
| Female              | 131 (48.7%)    | 123 (46.2%)        |
| <b>Race n (%)</b>   |                |                    |
| Asian               | 9 (3.3%)       | 10 (3.8%)          |
| Black               | 52 (19.3%)     | 51 (19.2%)         |
| Caucasian           | 189 (70.3%)    | 175 (65.8%)        |
| Other               | 19 (7.1%)      | 30 (11.3%)         |
| <b>Age (years)</b>  |                |                    |
| Median              | 11.0           | 11.0               |
| Range               | 3.0 – 18.0     | 3.0 – 18.0         |
| <b>Weight (kg)</b>  |                |                    |
| Median              | 34.6           | 37.4               |
| Range               | 12.7 – 122.2   | 10.9 – 126.1       |

**Table 13 Reviewer's Sensitivity Analysis: Study 003 FAS Full Effects Model (SAP Full Model)**

| <b>Wong-Baker FACES score</b><br>ANOVA with trt, age_grp, trt*age_grp, center, trt*center, body_site, trt*body_site, procedure, trt*procedure |  |                        |
|---|--|------------------------|
|   | <b>LHM (N=289)</b>   | <b>PLACEBO (N=285)</b> |
| <b>LS Mean (SE)</b>   | 1.73 (0.10)  | 2.02 (0.10)            |
| <b>Diff. from PBO (SE)</b>  | -0.29 (0.14)   |                        |
| <b>95% Confidence Interval for the Difference</b>   | (-0.57, -0.01)   |                        |
| <b>p-value*</b>   | <b>0.0389</b><br><0.0001<br>0.2992<br>0.0240<br>0.4402<br>0.0160<br>0.7189<br>0.0051<br>0.3542 |                        |

LSMeans and p-values calculated from ANOVA model:  $Y = \text{trt} + \text{age\_grp} + \text{trt*age\_grp} + \text{center} + \text{trt*center} + \text{body\_site} + \text{trt*body\_site} + \text{procedure} + \text{trt*procedure}$ .

\*P-values correspond to treatment, age group, treatment-by-age group, center, treatment-by-center, body site, treatment-by-body site, procedure, treatment-by-procedure effects, respectively.

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**Table 14 Reviewer's Sensitivity Analysis: Study 003 FAS (SAP Reduced Model)**

| Wong-Baker FACES score<br>ANOVA with trt, age_grp, trt*age_group, body_site, procedure |  |                 |
|--|--|-----------------|
|  | LHM (N=289)                                    | PLACEBO (N=285) |
| LS Mean (SE)   | 1.72 (0.09)                                    | 2.06 (0.09)     |
| Diff. from PBO (SE)  | -0.34 (0.12)                                   |                 |
| 95% Confidence Interval for the Difference   | (-0.58, -0.10)                                 |                 |
| p-values*  | 0.0062<br><0.001<br>0.2588<br>0.0469<br>0.0063 |                 |

LSMeans and p-values calculated from ANOVA model:  $Y = \text{trt} + \text{age\_grp} + \text{trt} * \text{age\_grp} + \text{body\_site} + \text{procedure}$ .  
\*P-values correspond to treatment, age group, treatment-by-age group, body site, procedure effects, respectively.

**Table 15 Reviewer's Sensitivity Analysis: Study 003 FAS Main Effects Model**

| Wong-Baker FACES score<br>ANOVA with trt, age_grp, center, body_site, procedure |  |                 |
|---|--|-----------------|
|   | LHM (N=289)                                    | PLACEBO (N=285) |
| LS Mean (SE)  | 1.71 (0.09)                                    | 2.05 (0.09)     |
| Diff. from PBO (SE)   | -0.34 (0.12)                                   |                 |
| 95% Confidence Interval for the Difference                                      | (-0.58, -0.10)                                 |                 |
| p-value*  | 0.0058<br><0.001<br>0.0235<br>0.0169<br>0.0031 |                 |

LSMeans and p-values calculated from ANOVA model:  $Y = \text{trt} + \text{age\_grp} + \text{center} + \text{body\_site} + \text{procedure}$ .  
\*P-values correspond to treatment, age group, center, body site, procedure effects, respectively.

**Table 16 Reviewer's Sensitivity Analysis: Study 003 FAS Selected Effects Model**

| Wong-Baker FACES score<br>ANOVA with trt, age_grp, trt*age_grp, procedure, trt*procedure |   |                 |
|--|---|-----------------|
|  | LHM (N=289)   | PLACEBO (N=285) |
| LS Mean (SE)   | 1.69 (0.09)   | 2.02 (0.09)     |
| Diff. from PBO (SE)  | -0.33 (0.13)  |                 |
| 95% Confidence Interval for the Difference   | (-0.58, -0.08)  |                 |
| p-value*   | <b>0.0088</b><br><0.0001<br>0.2799<br><0.0001<br>0.9633 |                 |

LSMeans and p-values calculated from ANOVA model:  $Y = \text{trt} + \text{age\_grp} + \text{trt}*\text{age\_grp} + \text{procedure} + \text{trt}*\text{procedure}$ .  
\*P-values correspond to treatment, age group, treatment-by-age group, procedure, treatment-by-procedure effects, respectively.

**Table 17 Reviewer's Sensitivity Analysis: Study 003 ITT (Worst Possible Score Imputation) Main Effects Model**

| Wong-Baker FACES score<br>ANOVA with trt, age_grp, center, body_site, procedure |  |                 |
|---|--|-----------------|
|   | LHM (N=292)  | PLACEBO (N=287) |
| LS Mean (SE)  | 1.74 (0.09)  | 2.06 (0.10)     |
| Diff. from PBO (SE)   | -0.32 (0.12)   |                 |
| 95% Confidence Interval for the Difference                                      | (-0.56, -0.08)   |                 |
| p-value*  | <b>0.0104</b><br><0.0001<br>0.0136<br>0.0077<br>0.0052 |                 |

LSMeans and p-values calculated from ANOVA model:  $Y = \text{trt} + \text{age\_grp} + \text{center} + \text{body\_site} + \text{procedure}$ .  
\*P-values correspond to treatment, age group, center, body site, procedure effects, respectively.

**Table 18 Reviewer's Sensitivity Analysis: Study 004 FAS Full Effects Model (SAP Full Model)**

| Wong-Baker FACES score<br>ANOVA with trt, age_grp, trt*age_grp, center, trt*center, body_site, trt*body_site,<br>procedure, trt*procedure |   |                 |
|---|---|-----------------|
|   | LHM (N=260)   | PLACEBO (N=257) |
| LS Mean (SE)  | 1.53 (0.14)   | 1.75 (0.14)     |
| Diff. from PBO (SE)   | -0.22 (0.20)  |                 |
| 95% Confidence Interval<br>for the Difference   | (-0.61, 0.18)   |                 |
| p-value*  | 0.2828<br><0.0001<br>0.1697<br>0.0566<br>0.9317<br>0.4012<br>0.0047<br>0.1716<br>0.1899 |                 |

LSMeans and p-values calculated from ANOVA model:  $Y = \text{trt} + \text{age\_grp} + \text{trt}*\text{age\_grp} + \text{center} + \text{trt}*\text{center} + \text{body\_site} + \text{trt}*\text{body\_site} + \text{procedure} + \text{trt}*\text{procedure}$ .

\*P-values correspond to treatment, age group, treatment-by-age group, center, treatment-by-center, body site, treatment-by-body site, procedure, treatment-by-procedure effects, respectively.

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**Table 19 Reviewer's Sensitivity Analysis: Study 004 FAS (SAP Reduced Model)**

| Wong-Baker FACES score<br>ANOVA with trt, age_grp, trt*age_group, body_site, trt*body_site, procedure |  |                 |
|---|--|-----------------|
|   | LHM (N=260)                                    | PLACEBO (N=257) |
| LS Mean (SE)  | 1.72 (0.09)                                    | 2.06 (0.09)     |
| Diff. from PBO (SE)   | -0.34 (0.12)                                   |                 |
| 95% Confidence Interval for the Difference  | (-0.58, -0.10)                                 |                 |
| p-values*   | 0.1171<br><0.001<br>0.2677<br>0.9825<br>0.0416 |                 |

LSMeans and p-values calculated from ANOVA model:  $Y = \text{trt} + \text{age\_grp} + \text{trt}*\text{age\_grp} + \text{body\_site} + \text{trt}*\text{body\_site} + \text{procedure}$ .

\*P-values correspond to treatment, age group, treatment-by-age group, body site, treatment-by-body site, procedure effects, respectively.

**Table 20 Reviewer's Sensitivity Analysis: Study 004 FAS Main Effects Model**

| Wong-Baker FACES score<br>ANOVA with trt, age_grp, center, body_site, procedure |   |                 |
|---|---|-----------------|
|   | LHM (N=260)                                     | PLACEBO (N=257) |
| LS Mean (SE)  | 1.47 (0.12)                                     | 1.83 (0.12)     |
| Diff. from PBO (SE)   | -0.36 (0.12)                                    |                 |
| 95% Confidence Interval for the Difference                                      | (-0.60, -0.12)                                  |                 |
| p-value*  | 0.0033<br><0.0001<br>0.0565<br>0.3433<br>0.1766 |                 |

LSMeans and p-values calculated from ANOVA model:  $Y = \text{trt} + \text{age\_grp} + \text{center} + \text{body\_site} + \text{procedure}$ .

\*P-values correspond to treatment, age group, center, tbody site, procedure effects, respectively.

**Table 21 Reviewer's Sensitivity Analysis: Study 004 FAS Selected Effects Model**

| Wong-Baker FACES score<br>ANOVA with trt, age_grp, trt*age_grp, procedure, trt*procedure |   |                 |
|--|---|-----------------|
|  | LHM (N=260)                                     | PLACEBO (N=257) |
| LS Mean (SE)   | 1.40 (0.10)                                     | 1.77 (0.10)     |
| Diff. from PBO (SE)  | -0.38 (0.14)                                    |                 |
| 95% Confidence Interval for the Difference   | (-0.65, -0.10)                                  |                 |
| p-value*   | 0.0072<br><0.0001<br>0.0968<br>0.0011<br>0.9367 |                 |

LSMeans and p-values calculated from ANOVA model:  $Y = \text{trt} + \text{age\_grp} + \text{trt} * \text{age\_grp} + \text{procedure} + \text{trt} * \text{procedure}$ .

\*P-values correspond to treatment, age group, treatment-by-age group, procedure, treatment-by-procedure effects, respectively.

**Table 22 Reviewer's Sensitivity Analysis: Study 004 ITT (Worst Possible Score Imputation) Main Effects Model**

| Wong-Baker FACES score<br>ANOVA with trt, age_grp, center, body_site, procedure |   |                 |
|---|---|-----------------|
|   | LHM (N=269)                                     | PLACEBO (N=266) |
| LS Mean (SE)  | 1.51 (0.12)                                     | 1.88 (0.12)     |
| Diff. from PBO (SE)   | -0.37 (0.13)                                    |                 |
| 95% Confidence Interval for the Difference                                      | (-0.63, -0.12)                                  |                 |
| p-value*  | 0.0042<br><0.0001<br>0.0676<br>0.6312<br>0.2546 |                 |

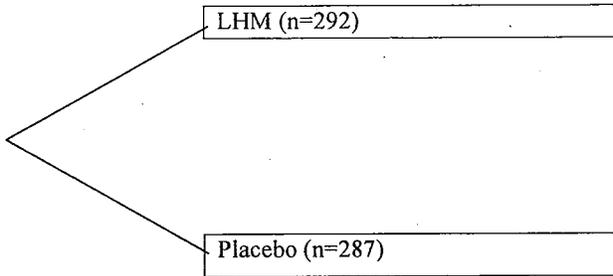
LSMeans and p-values calculated from ANOVA model:  $Y = \text{trt} + \text{age\_grp} + \text{center} + \text{body\_site} + \text{procedure}$ .

\*P-values correspond to treatment, age group, center, body site, procedure effects, respectively.

**Figure 1 Schematic of Study Design**

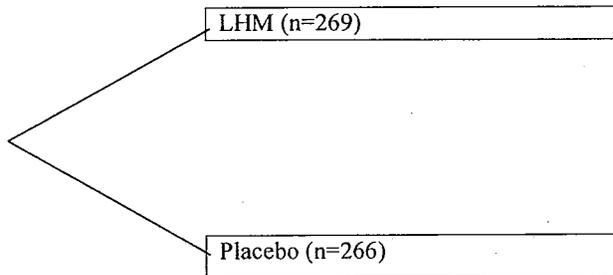
**Study 003:**

(N=579)  
Randomized 1:1



**Study 004:**

(N=535)  
Randomized 1:1



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**SIGNATURES/DISTRIBUTION LIST**

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Mathematical Statistician

**Date:** July 30, 2007

**Concurring Reviewer:** Dionne Price, Ph.D.  
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