

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-114

MEDICAL REVIEW(S)



**FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products**

DEPUTY DIVISION DIRECTOR REVIEW AND BASIS FOR ACTION

DATE: August 14, 2007

LETTER DATE: November 21, 2006

DRUG: Zingo (Lidocaine hydrochloride monohydrate) powder
for intradermal injection

NDA: 22-114 (b)(2)

SPONSOR: Anesiva, Inc.

DOSAGE STRENGTH: 0.5 mg

INDICATION: For use on intact skin to provide local analgesia
venipuncture or intravenous cannulation in patients 3
years of age and older

ACTION
Approval

ADDITIONAL INFORMATION REQUIRED FOR APPROVAL
None

BASIS FOR RECOMMENDATION

1. Substantial evidence of efficacy from two adequate and well-controlled trials
2. Acceptable risk benefit assessment
3. Adequate product development, specifications and controls.

Background

The applicant has submitted a 505(b)(2) application for Zingo, a single-use, disposable, drug-device combination intended to deliver 0.5 mg of powdered lidocaine hydrochloride monohydrate particles through the stratum corneum of intact skin into the epidermis. Zingo is

intended to provide local analgesia prior to venipuncture or cannulation procedures for use by healthcare providers licensed to administer human drugs. Studies have been submitted in support of efficacy for use in pediatric patients three years of age and older. b(4)

The applicant is referring to the findings of safety and efficacy from the approved products Synera™ and Lidoderm® in this 505(b)(2) application. The applicant references general information on the nonclinical and clinical pharmacology of lidocaine. Much of the proposed package insert is based on language from the Synera label. Synera™ (lidocaine 70 mg and tetracaine 70 mg) is a peel and stick topical anesthetic patch designed to provide local dermal analgesia for superficial venous access procedures. Lidoderm (lidocaine patch 5%) is indicated for the pain of post-herpetic neuralgia.

There are nine clinical studies in the current submission. Five clinical studies (3268-3-003-1, 3268-3-004-1, 3268-2-002-1, 3268-4-400-001, and 3268-4-401-001) were conducted to demonstrate safety and efficacy in the prevention of pain following peripheral venous cannulation or venipuncture in children. Two additional safety and efficacy studies (3268-1-100-001 and 3268-1-102-001) were conducted in adults utilizing the same dose and pressure as for the pediatric population. An open-label study to determine the sound emission levels produced by Zingo was conducted in healthy adult volunteers (3268-1-005-1). One pharmacokinetic study (3268-1-101-001) was also conducted. Overall, about 800 pediatric subjects and 200 adult subjects were exposed to Zingo in the above indicated clinical studies.

Chemistry, Manufacturing and Controls

Dr. Pandu Soprey of CDRH has performed the review of the device. The delivery system was developed to deliver dry powdered material through the skin utilizing pressurized helium to accelerate the particles. The system used for the delivery of the lidocaine powder was originally developed in 1996 by PowderJect Technologies, Inc., a subsidiary of PowderJect Pharmaceuticals. The final device configuration is a single-use disposable system comprised of the following major components: button, cover, silencer cover, housing, retainer clip (two total), compliant ball spacer, expansion chamber, nozzle, cassette assembly containing 0.5 mg lidocaine hydrochloride monohydrate (sized powder), filter, silencer foam, spring, helium gas cylinder (pressurized at 21 bar±1 bar). Several models of the delivery system were developed, and the final two versions of the prototype (ND5.3 and ND5.3A) were utilized in Phase 2 and 3 clinical trials listed. Devices filled with 0.25 or 0.5 mg lidocaine powder and pressurized with helium gas (20-40 bar) were explored for efficacy and safety.

The design of the device includes a safety interlock that prevents the device from being inadvertently actuated prior to appropriate device placement. Pressing the device nozzle against the skin releases the safety interlock, the button is then depressed to actuate the device. Actuation occurs when the depressed button breaks the tip of a micro-cylinder causing the helium gas to flow into the housing. As the gas pressure increases within the housing, the drug cassette film ruptures and the gas expands through the cassette and nozzle, entraining and accelerating the lidocaine powder particles. The momentum of the powder particles carries them out of the nozzle.

and into the skin, while the gas flows out of the nozzle, through the silencer and exhausts from the bottom of the cover.

Compatibility studies focused on the potential leachables from the [redacted]. The studies tested for volatile organic compounds, semi-volatile organic compounds and non-volatile organic compounds. [redacted]

b(4)

The levels of these compounds extracted from the sealed cassettes are very low and therefore there is no expected impact to the drug product. The release and stability data show that levels of lidocaine degradation products are low and do not significantly increase over time. This data supports that there is no apparent chemical reaction to generate detectable degradation products from any interactions between the lidocaine powder and the sealed cassettes. The extractable studies found that under normal storage conditions and use, the container is compatible with the drug product.

Microbial levels are monitored throughout manufacturing. Testing the lidocaine for microbial limits and endotoxin levels, manufacturing, testing, packing, and shipping of filled cassettes, final device assembly and packaging, and sterilization are performed by individual companies on behalf of the applicant. The lidocaine-filled cassette is assembled into the device within [redacted]

b(4)

All testing results have been within the specifications set by the applicant. The applicant proposes to package each device in an individual foil/clear pouch and then a bubble-wrap pouch with 12 devices per carton.

Dr. Soprey has concluded that the design, technological characteristics, safety, manufacturing and performance characteristics of the proposed Zingo autoinjector (device) are safe and effective for use as indicated.

Dr. William M. Adams has performed the CMC review. He notes that all manufacturing and control facilities meet cGMP requirements. The drug substance is lidocaine hydrochloride monohydrate (LHM) as a sized powder with a 40 micrometer nominal particle size. The starting material is adequately characterized in a type II DMF [redacted]. For the drug substance, drug-filled cassette and device with sterile LHM, the manufacturing processes, acceptance specification, release specifications, are acceptable. All analytical methods have been described in adequate detail and are validated and all criteria have been justified by the development studies, historical batch analysis data and the stability information. Stability studies performed at ICH conditions are adequate to support the proposed label storage statement of [redacted]

b(4)

For the device with sterile lidocaine hydrochloride monohydrate, quality standards have been established. Specifications for cassette acceptance, release of non-sterile lidocaine product and sterile lidocaine product were established to address identity purity, degradants, device function, emitted dose, foreign particulates, sterility assurance and bacterial endotoxins.

The request for categorical exclusion under 21 CFR25.34(c) in that Zingo will not significantly increase the environmental exposure to drug or device materials is adequately justified.

Three comparability protocols for manufacturing scale-up and a facility change within the firm, manufacturing scale-up for nonsterile device, and for justifying a new supplier of _____ were submitted and considered adequate to implement future CMC changes.

b(4)

Dr. Adams concludes that all approvability issues have been adequately resolved and recommends approval from the CMC viewpoint.

Nonclinical Pharmacology

Dr. Gary Bond performed the nonclinical pharmacology and toxicology review. Dr. Bond found the potential for systemic absorption is minimal, based upon levels seen with administration of the reference drugs (Synera™ and LIDODERM®), as seen in the following table from Dr. Bond's review.

Table 1

Comparison of Products

| Product | Lidocaine in Product | Lidocaine Delivered to Patient | Plasma Levels Following Treatment |
|-----------------------|----------------------|--------------------------------|--|
| Sterile LHM Product | 0.41 mg | 0.28-0.32 mg | <5 ng/mL ^a |
| Synera™ | 70 mg | 1.7 mg | <5 ng/mL ^a 63 ng/mL ^b |
| LIDODERM® (3 patches) | 2100 mg | 64 mg | 130 ng/mL |

Best Possible Copy

^a Following one application in adults.

^b Following one application in children (4 months to 12 years).

Dr. Bond also notes that safety for the route of application of the proposed drug product has been demonstrated nonclinically in local tolerance studies assessing dermal irritation and phototoxicity, including exposure greater than expected in clinical use. Three multi-dose local tolerance studies were performed with testing that included four administrations to separate sites per day on six days over a 28 day period; two administrations to the same site at various intervals over a 24 hour period; and twelve administrations to a single site over 1 hour. There were no clinical signs of discomfort. There were reversible dermal responses with the most severe effects occurring with use of PowderJect® devices with specifications in excess of the final proposed product. Evaluation of an intentionally relatively severe dermal response found that the effects were limited to the stratum corneum, epidermis, and papillary dermis, distanced from arterioles and venules that approach the dermis from the subcutaneous layer. Nonclinical evaluation of antiseptic pre-swabbing of the site of injection with alcohol or Betadine provided no indication that this common clinical practice will have an impact on the dermal response to the drug product. The drug product was also shown not to be phototoxic in hairless mice.

A 14-day repeat-dose dermal toxicology study in minipigs using 1, 2, or 3 actuations of the to-be-marketed drug product to the same site for 14 days followed by the same actuations pattern to

new skin sites for 14 days did not produce any evidence of systemic toxicity, local tissue irritation, or histopathological evidence of damage to the site of application compared to an untreated site.

Helium in the device canister and non-drug particulates were evaluated in several nonclinical in vitro studies including actuation into glass containers and pig and human cadaver skin, found no evidence for any health hazards relative to local and systemic exposure from the proposed drug product under specified conditions of use. Virtually all of the non-drug particulates evaluated in deposition studies were confined to the epidermal layers and will be removed by epidermal sloughing.

Clinical Pharmacology

The clinical pharmacology review was performed by Dr. Srikanth Nallani. The clinical pharmacology program for this product consists of data from a Phase 1 safety, tolerability, and pharmacokinetics study conducted in 38 adults. Following administration of a single dose to the antecubital fossa, blood samples were collected at 0 minutes, and at 1, 3, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, and 240 minutes. Using a validated analytical method, lidocaine, drug concentrations were below the limits of detection (5 ng/mL) in all treated subjects at every time point in the study. Dr. Nallani concluded that there is no meaningful systemic absorption of lidocaine.

Efficacy

The clinical review was conducted by Dr. Howard Josefberg and the statistical review was performed by Dr. Yongman Kim. Seven efficacy trials were submitted in support of this application. Two of these studies used the to-be-marketed product and are considered adequate and well-controlled, efficacy trials, Studies 3-003-1 and 3-004-1.

Studies 3-003-1 and 3-004-1 were identically designed, single-dose, double-blind, placebo-controlled, parallel group studies. Each study was to have enrolled 504 pediatric patients ages three to 18 years, with sufficient cognitive skills to use the Wong-Baker FACES (WBF) pain rating scale, the primary outcome measure. Consent was provided by parents or legal guardians with assent sought from the patients. Patients were scheduled to undergo venipuncture or peripheral venous cannulation (IV) at the antecubital fossa or back of the hand. Subjects were replaced if the venipuncture or IV placement failed. Secondary outcome measures included a 100-mm VAS, analyses of the WBF scores by age group, parent's assessment of child's pain using a 100-mm VAS, and success rate of venipuncture or venous cannulation. The age ranges for the secondary analyses were 3 to 7 years, 8 to 12 years and 13 to 18 years. Details of the statistical plans can be found in the review by Dr. Kim. The statistical analysis plan was amended prior to breaking of the blind. The first two protocol amendments were added prior to study initiation and the third amendment, added after enrollment had begun, were not of a nature to require exclusion of patients enrolled prior.

The applicant modified the instructions for the WBF scale, choosing to replace the standard instructions with those of the Faces Pain Scale-Revised (FPSR) instructions using the

justification that in their opinion, children do not pay attention to verbatim verbal instructions and that there was no need to re-establish construct validity of the instrument. The two scales have somewhat different face images. The instructions for the WBF are:

Explain to the child that each face is for a person who feels happy because he has no pain (hurt) or sad because he has some or a lot of pain. Face 0 is very happy because he doesn't hurt at all. Face 1 hurts just a little bit. Face 2 hurts a little more. Face 3 hurts even more. Face 4 hurts a whole lot, but Face 5 hurts as much as you can imagine, although you don't have to be crying to feel this bad. Ask child to choose the face that best describes how he/she is feeling.

The instructions from the FPSR are:

These faces show how much something can hurt. This face [point to the left-most face] shows no pain. The faces show more and more pain [point to each from left to right] up to this one [point to right-most face]—it shows very much pain. Point to the face that shows how much you hurt right now.

An evaluation was requested by the Study Endpoints and Label Development (SEALD) team to determine the significance of this substitution. The SEALD review by Dr. Ann Marie Trentacosti concluded:

... that the content validity of the modified instructions has not been substantiated in order to determine that the revised instructions are acceptable. The sponsor's justification of the instrument modification is primarily based upon the opinion that children do not pay attention to verbatim verbal instructions and in the establishment of construct validity of the instrument. However, the sponsor has not shown that the new instructions are appropriate and understandable for the target population. Establishing content validity is especially important for the proposed target population of children ages ≥ 3 to 18 year of age in which one set of instructions may not be appropriate for all ages.

In addition, since a modified version of the Wong-Baker FACES scale is utilized in the clinical trials, it is inaccurate for the sponsor to refer to the scale by this name in labeling. If efficacy statements concerning this modified instrument are included in the label, a more generic description (i.e. faces pain scale) should be considered.

Upon further discussion with the Dr. Trentacosti and Dr. Laurie Burke, it was noted that while the modified instructions had not been specifically validated with the particular faces from the WBF scale, the validity of the scale was not likely to have been compromised given that the instructions were in fact from another pain scale that also relied on the choice of six face images. Had the modified outcome measure incorporated instructions from measurement instruments not originally intended to measure the same construct and the same population, using very similar methods, it would be true that there could be no confidence that the measure could provide valid data. However, this was not the case and, in my opinion, the use of the WBF scale pictures with the FPSR instructions is acceptable in this setting.

The results of Studies 3-003-1 and 3-004-1 demonstrated a statistically significant difference in favor of the active treatment over placebo. The outcome of these analyses were confirmed by Dr. Kim. The results of the primary efficacy analysis are demonstrated in Table 2 taken from Dr. Josefberg's review. As shown, the size of the treatment effect is not particularly large in either study, although consistent across the two studies.

Table 2

Final Device Studies, Modified Wong-Baker FACES Score (ITT)

| | 3-003-1 | | 3-004-1 | |
|-------------------------|------------------|----------------------|------------------|----------------------|
| | LHM (N = 292) | Placebo (N = 287) | LHM (N = 269) | Placebo (N = 266) |
| Adjusted Mean, LSM | 1.77 | 2.10 | 1.38 | 1.77 |
| Standard Error of LSM | 0.09 | 0.09 | 0.09 | 0.09 |
| Difference in LSMs (SE) | -0.33 (0.13) | | -0.39 (0.13) | |
| p-value | 0.011 | | 0.003 | |
| 95% Confidence Limits | -0.58, -0.08 | | -0.65, -0.13 | |

Source: Study 3-003-1 Tables 11.1.10 and 5.1.1B, Study 3-004-1 Tables 11.1.10 and 5.1.1B in Section-14

Table 3, taken from Dr. Josefberg’s review, demonstrates the result of the secondary analysis of the pain scores measured by VAS in older patients between the ages of 8 and 18. The VAS scale is not considered appropriate for young children, and a cut-off period of 8 years is reasonable. These results confirm the findings from the modified WBF scores, there is an overall small, but consistent difference in average pain scores favoring the active treatment over placebo.

Table 3

Final Device Studies, Subject VAS (Ages 8 to 18)

| ITT Population | 3-003-1 | | 3-004-1 | |
|-------------------------|------------------|----------------------|------------------|----------------------|
| | LHM (N = 206) | Placebo (N = 200) | LHM (N = 183) | Placebo (N = 185) |
| Adjusted Mean, LSM | 22.62 | 31.97 | 16.58 | 21.47 |
| Standard Error of LSM | 1.80 | 1.82 | 1.80 | 1.78 |
| Difference in LSMs (SE) | -9.35 (2.56) | | -4.89 (2.53) | |
| p-value | <0.001 | | =0.054 | |
| 95% Confidence Limits | -14.4, -4.31 | | -9.87, 0.09 | |

Source: Study 3-003-1 report Tables 11.1.11 and 5.2.1 Study 3-004-1 Tables 11.1.10 and 5.1.1B

One additional relevant secondary analysis is the Parent Assessment of Child’s Pain which used a 100 mm VAS to measure the pain, as shown below. The findings of this analysis were consistent with the previous two.

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Table 4

Final Device Studies, Parent Assessment of Child's Pain, 100-mm VAS, Ages 3-18

| ITT Population | 3-003-1 | | 3-004-1 | |
|-------------------------|------------------|----------------------|------------------|----------------------|
| | LHM (N = 292) | Placebo (N = 287) | LHM (N = 269) | Placebo (N = 266) |
| Adjusted Mean, LSM | 21.69 | 28.92 | 16.66 | 22.97 |
| Standard Error of LSM | 1.54 | 1.54 | 1.44 | 1.45 |
| Difference in LSMs (SE) | -7.24 (2.18) | | -6.31 (2.04) | |
| p-value | ≈0.001 | | ≈0.002 | |
| 95% Confidence Limits | -11.5, -2.96 | | -10.3, -2.29 | |

Source: CSR 3-003-1 Table 5.4.1B, Section-14, CSR 3-004-1 Table-5.4.1, Section 14

Dr. Josefberg explored the effect of different doses of lidocaine. 0.5 mg and 1.0 mg, and different device pressures, 20 barr and 40 barr, tested with earlier device prototypes. There was no advantage to using more than the 0.5 mg dose and the 20 barr pressure.

Time to onset and duration of effect were explored in two of the adult studies,

Study 2-002-001 was very similar in design to Studies 3-003-1 and 3-004-1 except for use of an earlier device, ND5.3, only subjects scheduled for back-of-hand venipuncture were enrolled (not IV), and the primary efficacy analysis incorporated age-based outcome scales. The results of this study appeared comparable to the others, but as Dr. Josefberg notes, there are outstanding statistical concerns that would preclude use of this study as direct support for efficacy.

Study 4-400-001, a double-blind, placebo-controlled, parallel-group pediatric study, did not provide support for efficacy. However, this single site study conducted in Poland had data integrity issues and was not considered further with regard to efficacy.

The following studies were conducted in adult patients or volunteers. Study 1-102-001, was a double-blind, placebo-controlled, within-subject, two-period crossover, dose-ranging study, enrolling adult volunteers. The data from this study failed to statistically separate treatment groups for the proposed efficacy claim, using the to-be-marketed dose (lidocaine 0.50-mg/21-bar) even with an analysis of an efficacy evaluable population. As shown in Table 4, adapted from Dr. Josefberg's review, there was data to suggest that a 1 to 3-minute treatment-to-venipuncture (TTV) interval may be better than longer intervals (5 or 10-minutes).

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Table 5
Study 1-102-1 Applicant's Primary Efficacy Findings (Efficacy Evaluable Population)
Difference in VAS between Active and Placebo Treatments

| Treatment Group | N | Mean SE | Median | Range | 95% CI | P-Value |
|-------------------------------|----|-------------|--------|---------|----------------|---------|
| <u>0.50-mg/20-bar vs. PBO</u> | | | | | | |
| Total | 79 | -2.7 ± 3.0 | -3.0 | -54, 77 | (-8.7, +3.2) | 0.364 |
| 1-min | 20 | -12.7 ± 4.7 | -7.0 | -54, 23 | (-22.4, -3.0) | 0.013 |
| 3-min | 19 | 4.6 ± 7.5 | +3.0 | -40, 77 | (-11.0, +20.3) | 0.542 |
| 5-min | 20 | -5.1 ± 4.9 | -3.0 | -46, 35 | (-15.3, +5.2) | 0.315 |
| 10-min | 20 | 2.5 ± 6.4 | +2.5 | -42, 70 | (-11.0, +16.0) | 0.702 |

Source: Table 14.1, 1-102-001 CSR

Study 1-100-001 was a double-blind, placebo-controlled, two-period crossover, dose-ranging study, enrolling 272 adult volunteers. This study explored two device pressures (20-bar and 40-bar) and two lidocaine dose (0.25-mg and 0.50-mg), along with eight different treatment-to-venipuncture intervals were studied (1, 3, 5, 10, 15, 20, 30 and 60-minutes). The primary efficacy measure was subjects' rating of venipuncture-induced pain, using 100-mm VAS. The results suggested that the lidocaine 0.50-mg dose was more effective than the 0.25-mg dose, the 40-bar pressure as more effective than the 20-bar pressure, onset of dermal analgesia is within one to three minutes post-treatment, and by the ten-minute timepoint post-treatment there was substantially less difference between treatment groups.

Efficacy Conclusions

There is replicated evidence of efficacy of the 0.5 mg lidocaine dose delivered with a 20-bar device as compared to placebo in pediatric patients undergoing venipuncture or IV cannulation at the back of the hand or antecubital fossa.

Safety

Overall, 1031 patients/subjects were exposed to a 0.5 mg lidocaine dose via a device with 20 bars of pressure, with 1065 patients/subjects exposed to a sham 20-bar device. The demographic distribution for age, and gender are presented in Table 55 modified from Dr. Josefberg's review. There were slightly more male subjects than female. There was a good representation of patients ages 3-7 years (21%), 8-12 years (21%), and 13-18 years (24%). Approximately 83% of subjects were Caucasian.

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Table 6
Demographic Characteristics, ND5.3a and ND5.3 Studies (ITT Population)

| CHARACTERISTIC | ADULT | AND | PEDIATRIC |
|--------------------|-------------------|------------------------|-------------------|
| | LHM N=1389 (%) | PLACEBO- N=1282 (%) | ALL N=2260 (%) |
| GENDER | | | |
| MALE (%) | 736 (53.0) | 663 (51.7) | 1166 (51.6) |
| FEMALE (%) | 653 (47.0) | 619 (48.3) | 1094 (48.4) |
| AGE (YEARS) | | | |
| MEAN \pm SD | 18.9 \pm 14.5 | 18.6 \pm 14.4 | 15.8 \pm 12.5 |
| RANGE | 3-75 | 3-75 | 3-75 |
| 3-7 | 287 (20.7) | 271 (21.1) | 558 (24.7) |
| 8-12 | 290 (20.9) | 280 (21.8) | 570 (25.2) |
| 13-18 | 336 (24.2) | 311 (24.3) | 640 (28.3) |
| 19-44 | 357 (25.7) | 312 (24.3) | 369 (16.3) |
| 45-65 | 112 (8.1) | 102 (8.0) | 116 (5.1) |
| >65 | 7 (0.5) | 6 (0.5) | 7 (0.3) |
| ETHNICITY | | | |

SOURCE: ISS TABLE 2.4.7, PAGE-28 AND ISS DATASET DEMOG-D.XPT

There were no substantial safety concerns for the final device configuration. Throughout the development program, there were no deaths. Serious adverse events (SAEs) were reviewed in detail by Dr. Josefberg. Four patients suffered SAEs with early device configurations while eight patients suffered SAEs with late device configurations. None of the SAEs appeared to be in any way related to administration of study drug, but rather, to significant underlying medical conditions. The SAEs reported in patients from late device studies included, abnormal chest x-ray, chest infection, exacerbation of ulcerative colitis, anaphylactic reaction to radiographic contrast, diabetic ketosis, spine fracture, leukocytosis, dehydration, hospitalization, post-extubation laryngospasm, and migraine.

Given the study designs with most studies of only one treatment, dropouts from the studies were generally not treatment related, or relevant. See Dr. Josefberg's review for details. Dr. Josefberg does note one case of an important adverse event occurring following use of an early device configuration (40 barr, larger particle size) in a 10-year old female patient, sloughing of skin at the site of application of study drug following Grade-4 erythema. She recovered the following week. The device used a higher pressure and the lidocaine had a larger particle size than the current formulation which may have contributed to the adverse event. Similar events were not reported with the final device configuration. He also notes one case in a 15-year old patient who was treated with the active, final device. The patient developed cellulitis at the site of an IV three days following outpatient surgery. The cellulitis was successfully treated with Bactrim. Given that the Zingo treatment site was also the site of an IV, and the lack of other similar events reported in the database, it is unclear that there is a causal relationship between study drug and the cellulitis, although the possibility cannot be ruled out.

Table 7 from Dr. Josefberg's review describes the rating system for skin changes.

Table 7

Grading Scales for Assessment of Skin Changes (Late-Device Studies)

| Grade | Erythema | Edema | Pruritus | Hemorrhage/Petechiae |
|-------|---|--|-------------|---|
| 0 | No erythema | No edema | No pruritus | None |
| 1 | Very slight erythema (barely perceptible) | Very slight edema (barely perceptible) | Occasional | Up to 5 isolated petechiae |
| 2 | Well defined erythema | Slight edema (area edges well defined by raising) | Constant | Greater than 5 isolated petechiae |
| 3 | Moderate to severe erythema | Moderate edema (raised \approx 1-mm) | N/A | Many petechiae, with some coalescence |
| 4 | Severe erythema (beet red) to slight eschar formation | Severe edema (raised > 1 mm, extending beyond exposure area) | N/A | Numerous petechiae \pm pin-prick surface blood spots, or surface bleeding |
| 5 | N/A | N/A | N/A | Frank bleeding |

Source: ISS page-7, Table-1 and page-8, Table-2

Overall, of patients exposed to the final dose/pressure configuration, 60% had some degree of erythema at the site of active drug application, compared to 30% of patients who received the sham treatment. A total of 7.5% of patients treated with the active product had edema, compared to 3% of those treated with the sham. Four percent of the active patients had pruritus, compared with 3% of the placebo patients. Forty-four percent of the active patients had hemorrhage compared with 6% of the sham patients. Table 8, taken from Dr. Josefberg's review, demonstrates the frequency of the most severe skin site assessments, those occurring in the worst two grade levels of each category. The frequencies of the worst events are substantially lower than the overall skin assessment event rates.

Table 8

Safety Overview – Abnormal Post-Treatment Skin Assessment, Worst Two Grades

| | ND5.3A and ND5.3 Controlled Pediatric Studies | | | |
|---|---|-----------------------|------------------|----------------------|
| | LHM N=1389 (%) | Placebo N=1282 (%) | LHM N=561 (%) | Placebo N=553 (%) |
| Number (%) of Subjects with Abnormal Skin Assessment | | | | |
| Erythema | 29 (2.1) | 0 (0.0) | 4 (0.7) | 0 (0) |
| Edema | 2 (0.1) | 0 (0.0) | 0 (0) | 0 (0) |
| Pruritus | 26 (1.9) | 18 (1.4) | 1 (0.2) | 1 (0.2) |
| Hemorrhage/Petechiae | 12 (0.9) | 0 (0.0) | 9 (1.6) | 0 (0) |

Source: Data listings 14.3.2.1, 14.3.3.1, 14.3.4, 14.4.1 and ISS Tables 7.2.1, 7.3.1, 7.4 and 7.5

There were few adverse events to report with a frequency of more than 0.5%. For events in patients who were exposed to the to-be-marketed dose and pressure, only nausea, vomiting, dizziness, and local reactions reached a frequency of 0.5% or more.

As noted in Dr. Josefberg's review, there were no notable changes in vital signs or laboratory values.

Discussion

There is adequate evidence of safe and well-controlled manufacturing processes for this novel drug-device combination. There is adequate clinical evidence of efficacy based on two adequate and well-controlled trials and no safety issues of concern. There is evidence of no detectable systemic exposure to lidocaine following use of this product. There were no nonclinical signals as a result of actuation of the device. Therefore, the overall risk-benefit balance is favorable for approval of Zingo to provide local analgesia prior to venipuncture or cannulation procedures in patients over the age of 3 years, when used by healthcare providers licensed to administer human drugs.

Addendum: August 16, 2007

The applicant has requested a waiver from requirements to perform pediatric studies in patients less than three years of age. The applicant's primary argument is that the current device configuration is not appropriate for smaller patients. In considering the question of suitability of this product for use under the age of three years, the applicant's argument is not suitable to support a waiver. If the product were to be useful and fulfill a need in patients less than three years, it would be their responsibility to develop a suitable device. Rather, this device makes a loud popping sound when actuated. This can be difficult to explain to children less than three years, and impossible to explain to nonverbal children. The primary toxicity associated with the use of Zingo has been local skin irritation. While mild, there may be greater concerns with the skin of the very young. In addition, there are alternative topical lidocaine products that can be used to diminish the pain of IV cannulation or venipuncture. In particular, EMLA is approved as a topical anesthetic for use on normal intact skin for local analgesia, and is approved for use down to age) (gestation age of at least 37 weeks). Therefore, there is not a medical need for this product in patients under 3 years of age and a waiver of studies in these patients can be granted.

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CLINICAL REVIEW

Application Type 22-114
Submission Number 000
Submission Code Type 1 S

Letter Date 11/24/2006
Stamp Date 11/28/2006
PDUFA Goal Date 09/24/2007

Reviewer Name Howard Josefberg, M.D.
Review Completion Date 07/17/2007

Established Name Lidocaine Powder Delivery System
(Proposed) Trade Name Zingo™
Therapeutic Class Local anesthetic
Applicant Anesiva, Inc.

Priority Designation Standard

Formulation Topical
Dosing Regimen Single-dose use
Indication For use on intact skin to provide local
analgesia prior to venipuncture or
intravenous cannulation
Intended Population Pediatric

ABBREVIATIONS

| | |
|-----------------|---|
| ACF | Antecubital fossa |
| ANCOVA | Analysis of covariance |
| ANOVA | Analysis of variance |
| BOH | Back of hand |
| CFR | Code of Federal Regulations |
| CMC | Chemistry, Manufacturing and Controls |
| CMH | Cochran Mantel-Haenszel chi-square |
| CPMP | Committee for Proprietary Medicinal Products |
| CRF | Case report form |
| CRO | Contract research organization |
| CSR | Clinical study report |
| DAARP | Division of Analgesia, Anesthesia and Rheumatology Products |
| DACCADP | Division of Anesthetic, Critical Care and Addiction Drug Products |
| DB-PC | Double-blind, placebo-controlled |
| DB-PG | Double-blind, parallel-group study |
| DB-XO | Double-blind, crossover study |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders Fourth Edition |
| EOP2 | End-of-Phase-2 (Meeting) |
| FAP / FAS | Full analysis population |
| GCP | Good Clinical Practices (21CFR §§ 50, 56, and 312) |
| LHM | Lidocaine hydrochloride monohydrate |
| LSM (\pm SE) | Least-squares mean (\pm standard error) |
| MedDRA | Medical Dictionary for Regulatory Activities (Version 5.1 used) |
| ONDQA | Office of New Drug Quality Assessment |
| PI | Package Insert |
| PBO | Placebo |
| PCSA | Potentially clinically significant (laboratory) abnormality |
| pNDA | Pre-NDA (Meeting) |
| PT | Preferred Term (MedDRA) |
| RX | Treatment |
| SMQ | Standardized MedDRA Query |
| SOC | System organ class (MedDRA and WHO-ART) |
| TEAE | Treatment Emergent Adverse Event |
| TTV | Treatment-to-venipuncture [Interval between study treatment and venipuncture] |
| UDC | Urine drug screen (toxicology) |
| ULN | Upper limit of normal |
| WBF | Wong-Baker FACES pain rating scale |
| WHO-ART | World Health Organization – Adverse Reaction Terminology |
| WHO-DRL | World Health Organization - Drug Reference List |

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

[Pending CMC, CDRH and Pharmacology/Toxicology recommendations]

I recommend approval for NDA 22-114, for the pediatric population (ages 3 through 18), for the proposed indication, "...for use on intact skin to provide local analgesia prior to venipuncture or intravenous cannulation."

- The application provides substantial evidence of effectiveness for the proposed indication.
- The product has been shown to be safe for its intended use in the pediatric population.
- The proposed label requires substantial revision, because of implied and other unacceptable efficacy and Γ claims. These claims are, for the most part, based upon statistical analyses (of secondary efficacy data) of questionable appropriateness and rigor.

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1.2 Recommendation on Postmarketing Actions

No Phase-4 commitments are necessary, but the applicant should be urged to enroll adequate numbers of geriatric aged subjects in their upcoming adult efficacy trials.

1.3 Summary of Clinical Findings

Anesiva is referring to the Agency's findings of safety and efficacy for the approved products Synera™ (21-623) and Lidoderm® (20-612) in this 505(b)(2) application. The proposed label's Clinical Pharmacology, Warnings and Precautions sections are reproduced from Synera™ label.

1.3.1 Brief Overview of Clinical Program

The clinical data submitted in support of this application were generated from:

- Two Phase-3 double-blind, placebo-controlled, pediatric studies with the final-device (ND5.3A).
- Five Phase 2/3 controlled studies with the last device prototype (ND5.3); three in pediatric subjects, and two in adult subjects.
- Two open-label adult studies; one a pharmacokinetic study (ND5.3), the other an assessment of device sound levels (ND5.3A)
- Fourteen studies with (five) early device prototypes; these studies evaluated varying:
 - Device pressures
 - Lidocaine doses
 - Lidocaine particle sizes

Device

The final, to-be-marketed device, ND5.3A, was utilized only in Studies 3-003-1 and 3-004-1 (and a small open-label safety study). The six other late-device controlled trials, and the only PK study utilized the ND5.3 device. Drug delivery with the ND5.3A device is at 21.0-bar (± 1.0 -bar) pressure, while ND5.3 pressure was 20.0-bar (± 1.0 -bar). Anesiva contends that given the overlap in pressure ranges, no functional differences exist between devices. Dr. Soprey (CDRH) agrees.

Primary Efficacy Endpoint

The primary efficacy measure in Phase-3 trials was subjects' assessment of pain, caused by venipuncture or intravenous cannulation, one to three minutes after study drug administration. The primary measurement instrument was an applicant-constructed, non-validated hybrid of two similar instruments. (The Wong-Baker-FACES diagram was used with instructions from the Faces Pain Scale-Revised). Although content validity was not demonstrated for the modified instrument, I believe that the two scales and their respective instructions are conceptually very similar. While not

ideal, the modified instrument is acceptable. Furthermore, use of an instrument lacking content validity would be expected to bias against supportive efficacy findings, hindering the applicant's ability to demonstrate product efficacy.

1.3.2 Efficacy

Both final-device controlled studies support the applicant's efficacy claim. The application provides adequate evidence of product efficacy for the proposed indication, in the pediatric population. Data from the late (but not final) device trials are generally supportive. Both controlled adult (late-device) studies were dose-ranging trials, inadequately designed to demonstrate efficacy of the to-be-marketed product.

1.3.3 Safety

Zingo™ was shown to be safe and well tolerated. Safety was shown in the target (pediatric) population using the final commercial device (ND5.3A). The overall pediatric population included many patients with acute and chronic medical conditions, likely reflecting the product's target population.

Adverse events were mostly local to the treatment site, mild, and self-limited. SAEs and severe skin reactions were very rare. Systemic lidocaine exposure is not expected.

1.3.4 Dosing Regimen and Administration

Along with a series of diagrams demonstrating how to activate the device, the proposed label includes the following dosing instructions:

┌

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These dosing instructions are, for the most part acceptable; implied claims will need to be removed.

1.3.5 Drug-Drug Interactions

Drug-drug interactions are not anticipated, given the lack of systemic absorption with labeled, and also with anticipated clinical use. No drug-drug interaction studies were conducted.

1.3.6 Special Populations

Geriatric subjects were not well represented in the safety database. Only seven subjects older than 65 years received study drug. The Zingo™ product's safety profile could possibly be different for geriatric patients, because of age-related alterations in skin integrity. Efficacy differences, though theoretically possible, are not expected, however.

Alterations in dosing instructions are not necessary for patients with renal or hepatic impairment, given the lack of systemic absorption with labeled and with anticipated product use.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

2.2 Currently Available Treatment for Indication

- Several local anesthetic products are approved to reduce the pain of needle insertion, including:
 - EMLA® cream, a eutectic mixture of lidocaine and prilocaine, AstraZeneca Pharmaceuticals
 - Synera™, a self-heating patch containing a eutectic mixture of lidocaine and tetracaine, Ferndale Laboratories
- Other approved topical anesthetic products are sometimes used off-label, such as LIDODERM® (lidocaine patch 5%, approved for the treatment of post-herpetic neuralgia, Endo Pharmaceuticals).
-

Several products are under development, including other lidocaine products employing relatively new delivery mechanisms, though none include new active pharmaceutical ingredients (API).

2.3 Availability of Proposed Active Ingredient in the United States

Lidocaine hydrochloride, the active pharmaceutical ingredient, is widely available in the USA, from multiple manufacturers.

2.4 Important Issues with Pharmacologically Related Products

As of July 20, 2007 no similar products have been approved in the USA or European Union. That is, there are no approved products utilizing pressurized systems for the delivery of active drug.

2.5 Presubmission Regulatory Activity

Table 2-1: Pre-Submission Regulatory Activity

| Date | Event | Details |
|----------|-------------------|---|
| 04/24/01 | Change of sponsor | _____ to PowderJect Technologies, Ltd. |
| 10/17/02 | Type-C meeting | 505(b)(2) appropriate, CMC and Pharm/Tox issues, proposed PK study Skin sites to evaluate product in/on, delivery system concerns (pressure) Ages of pediatric subjects to be studied, evaluation of device noise |
| 02/13/03 | Type-C meeting | Lot-to-lot uniformity, evaluation of device with other drugs, CRF design Any serious skin damage, in any subject will suggest unacceptable risk Potential for particle embolism |
| 02/20/03 | Clinical hold | No data presented to quantify depth of penetration of particles and gas |
| 05/25/03 | Remove hold | Deficiency resolved, adequate data re: penetration depth submitted |
| 11/17/04 | EOP2 meeting | Sponsor should collect data re: degree and duration of anesthesia and analgesia in Phase-3 trials – Sponsor should study product use in wider variety of settings/procedures, and in a more varied population (>18 y/o) BioPharm – Agency will require pediatric PK data, given anticipated pediatric only indication, CMC and CDRH issues |
| 06/19/06 | Pre-NDA meeting | Acceptability of unvalidated hybrid pain scale, safety database size Structure and content of ISS and overall application, CMC/CDRH issues |

Source: Clinical reviewer

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

ONDQA and CDRH review teams raised no concerns that would preclude approval. Both review teams recommend an *approval* action.

The Chemistry review team found the CMC portion of the application to be acceptable. Adequate CMC information regarding the drug substance was submitted, and appropriate stability data to support expiration dating (of the drug/device combination) were provided. No concerns were identified regarding the device manufacturing process or manufacturing sites.

The final, to-be-marketed device, ND5.3A, was utilized only in Studies 3-003-1 and 3-004-1 (and a small open-label safety study). The six other late-device controlled trials, and the only PK study utilized the ND5.3 device. Anesiva describes the devices as nearly identical in construction and function, both delivering 0.50-mg lidocaine, b(4)
Drug delivery with the ND5.3A device is at 21.0-bar (± 1.0 -bar) pressure, while ND5.3 pressure was 20.0-bar (± 1.0 -bar).

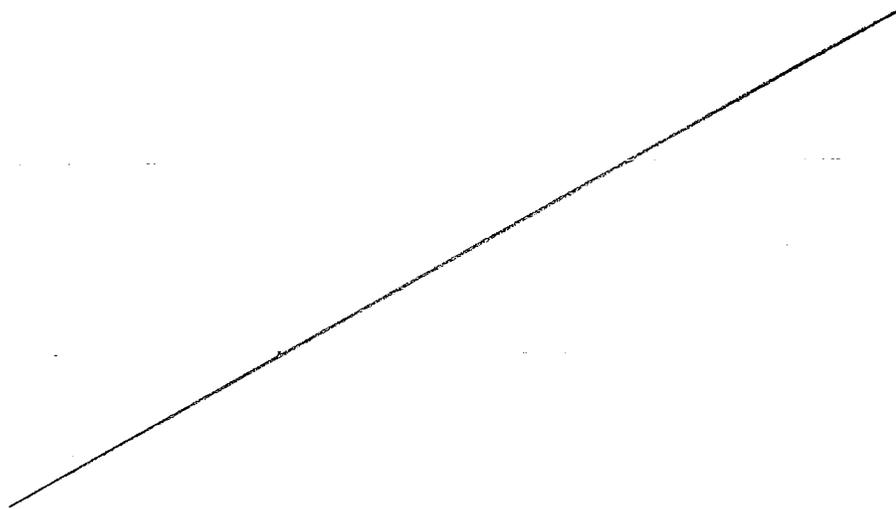
Anesiva contends, that given the overlap in actual pressure ranges, no significant difference would exist, between the ND5.3 and ND5.3A devices. Based upon preliminary assessment, Dr. Pandu Soprey (the CDRH reviewer) agrees, stating in his preliminary review:

The ND5.3A is a final modification of the ND5.3 device with changes in parts design. The changes were made to b(4)
and the changes were made to the spacer, actuation button, housing boss, nozzle retainers and silencer cover. Performance characteristics of ND5.3A are comparable to ND5.3. Both devices contain 0.5mg sterile LHM powder and the same gas pressure (20-bar). ND5.3A was used in Phase 2 and 3 clinical trials (pivotal trials). The ND5.3A is the final commercial configuration.

Key characteristics of the developmental (and final) devices are shown in Table 3-1 on page-9 (Anesiva ISS Table 2.2.4).

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Table 3-1: Zingo™ Developmental Devices



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- ^a Includes primary stability lots.
- ^b Sieved powders designated by sieve sizes. Particle size distribution of air classified powders produced from 2000 through Phase 3 determined by Aerosizer. Particle size distribution of air classified powders used in the primary stability lots determined by PSD3603.
- ^c Commercial configuration powder particle size distribution determined by PSD 3603.
- ^d Nominal mean particle size.

3.2 Animal Pharmacology/Toxicology

Dr. Bond concludes that the animal data, specifically, the minipig local tolerance studies, suggest limited potential for local toxic effects in humans, with product use as labeled. The potential for systemic absorption is minimal, based upon levels seen with administration of the reference drugs (Synera™ and LIDODERM®).

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4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

New Drug Application 22-114 was received on November 24, 2006. The application adhered to Common Technical Document (CTD) formatting conventions. The original NDA submission appeared to include most FDA-required items. Overall, the application was considered consistent with US regulatory requirements, and deemed acceptable for filing.

It was later discovered that safety data from the fourteen early-device trials had not been summarized or integrated in any way. Likewise, no electronic data were submitted for these fourteen studies.

This review is based on information included in the original NDA submission as well as:

- Materials and correspondence submitted to IND 54,740
- Applicant responses to information and data requests submitted in Amendments #001 through #008 loaded to the EDR on 01/09, 03/08, 03/16, 04/18, 05/10, 05/22, 06/19 and 06/27 (all in 2007). The contents of each amendment are listed in Table 12-1 in Section 0 (Appendix).
- No 120-day safety update was submitted. No studies were in progress as of application submission, nor have any new ones begun.
- ONDQA and CDRH reviews of this application
- Statistics, OPCB and Pharmacology/Toxicology reviews of this application
- Consultation responses from Cardio-Renal, ODS and DDMAC reviewers
- Two final DSI field reports (Drs. Zempsky and Sher), and two preliminary reports.

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4.2 Tables of Clinical Studies

Nine “late-device” studies were conducted; three with the to-be-marketed device (ND5.3A), and six with the final prototype (ND5.3). Seven were double-blind, placebo-controlled; two were open-label. Five of the controlled trials enrolled only pediatric subjects, while two enrolled only adults.

- Two single-dose, double-blind, placebo-controlled, parallel-group studies were conducted with the final, to-be-marketed product, both in pediatric subjects (3-003-1 and 3-004-1). Open-label sound assessment Study 1-005-1 also used the ND5.3A device.
- All five pediatric studies utilized a parallel group design; each subject received either active drug or placebo. The two adult trials (1-100-001 and 1-102-001) utilized a crossover design, in which each subject received active lidocaine once and placebo once.

Table 4-1 below summarizes relevant details from the nine late-device studies.

Table 4-1: Phase-2/3 (Late Device) Trials Reviewed for Safety and Efficacy Findings

| Study | 1-101-1 | 1-100-1 | 1-102-1 | 4-401-1 | 4-400-1 | 2-002-1 | 3-003-1 | 3-004-1 | 1-005-1 |
|-------------------|-------------------|--------------------|-------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Population | Adult | Adult | Adult | Pediatric | Pediatric | Pediatric | Pediatric | Pediatric | Adult |
| Objective | Safety/PK | Dose-ranging | Dose-ranging | Dose-ranging | Dose-ranging | Phase-3 | Phase-3 | Phase-3 | Sound levels |
| Device Used | ND5.3 | ND5.3 | ND5.3 | ND5.3 | ND5.3 | ND5.3 | ND5.3A | ND5.3A | ND5.3A |
| Pain Model | None | VP | VP | VP | VP | VP | VP/IV | VP/IV | None |
| Body Site | ACF | ACF | BOH | ACF | BOH | BOH | BOH/ACF | BOH/ACF | BOH/ACF |
| Number | 38 | 272 | 183 | 145 | 195 | 307 | 579 | 535 | 6 |
| Design | OL | DB-XO | DB-XO | DB-PG | DB-PG | DB-PG | DB-PG | DB-PG | OL |
| Dose/ Pressure | 0.5 mg/ 20 bar | 0.25 mg/ 20 bar | 0.5 mg/ 20 bar | 0.25 mg/ 20 bar | 0.5 mg/ 20 bar | 0.5 mg/ 20 bar | 0.5 mg/ 21 bar | 0.5 mg/ 21 bar | 0.5 mg/ 21 bar |
| | | 0.5 mg/ 20 bar | 0.5 mg/ 40 bar | 0.5 mg/ 20 bar | 0.5 mg/ 40 bar | 20 bar/ PBO | 21 bar/ PBO | 21 bar/ PBO | |
| | | 0.5 mg/ 40 bar | 20 bar/ PBO | 20 bar/ PBO | 20 bar/ PBO | | | | |
| | | 20 bar/ PBO | 40 bar/ PBO | | 40 bar/ PBO | | | | |
| | | 40 bar/ PBO | | | | | | | |

VP=venipuncture, IV=intravenous cannulation, ACF=antecubital fossa, BOH=back of hand

Source: Clinical reviewer

Table 12-2, beginning on page-126 summarizes the fourteen early device studies.

4.3 Review Strategy

For the efficacy review attention was focused on the two controlled final-device trials, Studies 3-003-1 and 3-004-1. Data from five additional late-device, controlled trials were also reviewed.

The safety review focused on the two applicant-defined databases; 'late-device studies' and 'early-device studies.'

4.4 Data Quality and Integrity

Data quality was adequate and no issues with integrity arose during review.

The initial application included no integrated presentation of the Phase-1 safety data, either as a standalone database, or with the Phase-2/3 data. After multiple requests, Amendment #007 was submitted (06/25/2007).

Adverse event elicitation and coding were acceptable. The application was readily navigable, though some early study reports were poorly written. Responses to information requests were generally prompt. Multiple written requests, and finally a teleconference, were necessary, however, in order to obtain an integrated summary of safety data from the early-device trials. This document arrived about four months after the initial request.

Clinical study reports for a number of the earliest trials were incomplete or unacceptably brief. This was also the case, however, for Phase-2 Study 4-400-001, a double-blind, placebo-controlled, parallel-group pediatric study conducted at a single site in Poland (in 2004, N=195). The original CSR, dated 03/31/04, was amended on 06/28/06. The amendment states, "The following sections are incomplete, as the previous sponsor did not provide the information in the report."

- Section 16.1.9, *Documentation of Statistical Methods*
- Section 16.1.10, *Documentation of Inter-Laboratory Standardization Methods and Quality Assurance Procedure*
- Section 16.1.3, *List of IRBs and Representative Written Information for Subject and Sample Consent Forms*: "The name of the independent ethics committee is not listed."

Section-16 is actually missing entirely from the CSR. The subsections listed above are not "incomplete." They do not exist. Thus, the integrity of the 4-400-001 data is questionable. These data were not needed in support of product efficacy, though, nor were they necessary to provide substantial evidence of product safety. (They have, however, been included in the integrated safety summary.) The application's other late-device study reports are complete, with no data integrity issues identified, thus the integrity of the overall application is not in question.

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4.4.1 DSI Clinical Inspections

Although the final DSI report is not yet available, preliminary findings suggest that no serious study conduct or data management issues were identified at the individual clinical centers. Incorrect coding was very rare, and no data management issues were identified. Four clinical sites were chosen for routine DSI inspection, based upon one or more of the following:

- Efficacy findings more strongly supportive than those from other study sites
- Considerably higher enrollment than most other sites
- A relatively high proportion of protocol deviations, screening failures or failed first venipuncture (or IV) attempts necessitating subject replacement (early discontinuation occurred very rarely in these single-session studies)
- Contract research organization

Table 4-2 lists the clinical sites for the two controlled final-device trials. For both trials, protocol deviation and screening failure rates varied little from site to site. The sites chosen for inspection (shaded), had considerably more supportive efficacy findings (than other sites), and/or enrolled larger numbers of subjects. For example, Dr. Zempsky's site (#12) enrolled over 25% of the 3-003-1 subjects, and had that study's most positive efficacy findings as well. Dr. Zempsky was also the designated primary investigator for 3-003-1.

Table 4-2: NDA 22-114 (Zingo™) Clinical Site Inspections

| Investigator | Center | Site # | N | p-value* |
|----------------------|---------------------------------------|--------|-----|----------|
| Study 3-003-1 | | | | |
| J. Bean-Litewski | Scott & White Memorial Hospital, TX | 01 | 98 | 0.061 |
| R. Kauffman | Children's Mercy Hospital, KC, MO | 05 | 99 | 0.953 |
| J. Koh | Oregon Health Science University | 06 | 95 | 0.923 |
| S. Malviya | University of Michigan | 07 | 52 | 0.095 |
| J. Rose | Children's Hospital Philadelphia | 08 | 83 | 0.548 |
| W. Zempsky | Connecticut Children's Medical Center | 12 | 152 | 0.043 |
| TOTAL 3-003-1 | Mean Enrollment = 96.5 | | 579 | 0.011 |

| Investigator | Center | Site # | N | p-value |
|------------------------|--|--------|-----|---------|
| Study 3-004-1 | | | | |
| | | 02 | 2 | NA |
| J. Finkel | Children's National Medical Center, DC | 03 | 106 | 0.783 |
| E. Krane and G. Hammer | Stanford University Medical Center Department of Anesthesia | 04 | 73 | 0.346 |
| M. Rossberg | Johns Hopkins Hospital, Anesthesia | 09 | 27 | 0.005 |
| M. Schmitz | Arkansas Children's Hospital | 10 | 100 | 0.507 |
| A. Rodarte | Children's Hospital, San Diego | 13 | 50 | 0.301 |
| E. Sarkis | Sarkis Clinical Trials, Gainesville, FL | 14 | 9 | 0.461 |
| B. Finkel | Aeroallergy Research Labs, Savannah, GA | 15 | 55 | 0.129 |
| L. Sher | Peninsula Research Associates, CA | 16 | 113 | 0.146 |
| TOTAL 3-004-1 | Mean Enrollment = 59.4 | | 535 | 0.003 |

b(4)

* Primary efficacy measure (FACES), active vs. placebo Source: Clinical reviewer

4.5 Compliance with Good Clinical Practices

All Phase-2 and Phase-3 trials utilized identical measures to ensure adherence to the Good Clinical Practice (GCP) guidelines established under the Declaration of Helsinki. Section 9.6 of each Phase-2/3 study report describes the measures taken to ensure ethical study conduct and data integrity:

- The study was designed to comply with the Good Clinical Practice guidelines
- An investigator meeting was held for each study, attended by investigators and site coordinators
- Study initiation meetings were conducted at each site, attended by key personnel
- All investigators and appropriate staff were trained in the correct use of the device
- Site visits were conducted periodically, to ensure adherence to these guidelines, to review source documentation, perform source data verification and cross check the data
- Telephone conferences were held, attended by the site coordinators and sponsor's representatives.
- The applicant had access to all records necessary to ensure the integrity of the data, and periodically reviewed the progress of the study with each Investigator.

Applicant management of trial data included:

- Data entry, verification, and validation were carried out using ClinTrial Version 4.1
- A double-entry method was used to ensure that the data (except comments) were transferred accurately from the CRFs to the database.
- Every modification in the database could be traced using an audit trail.
- A data checking plan was established to define all automatic validation checks, as well as supplemental manual checks, to ensure data quality.
- All discrepancies were researched until resolved.

Adverse events in early-device studies were coded using World Health Organization – Adverse Reaction Terminology (WHO-ART). Adverse events in late-device studies were coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 7.0).

Concomitant medication use was documented using the World Health Organization Drug Reference List (WHO-DRL, Version 97.4).

4.6 Financial Disclosures

Review of the investigator financial disclosure statements showed no investigators with reported (or otherwise apparent) conflicts of interest.

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5 CLINICAL PHARMACOLOGY

The Office of Clinical Pharmacology and Biopharmaceutics recommend an *approval* action for NDA 22-114. The pharmacokinetic data were considered acceptable and adequate for review. No deficiencies were identified. No comments for the applicant were provided or suggested.

The clinical pharmacology program consisted of a single safety, tolerability, and PK study (1-101-001) in 38 adults, ages 18 to 45. Each subject received a single dose of Zingo™ to the antecubital fossa of either the left or right arm. Blood samples were collected at 0 minutes, and at 1, 3, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, and 240 minutes. Plasma samples were analyzed for lidocaine employing a validated analytical method. Lidocaine drug concentrations were below the limits of detection (5 ng/mL) in all treated subjects, at every time point. Pharmacokinetic parameters could not be estimated.

No further pharmacokinetic studies are necessary, according to OPCB, because "... there is no meaningful systemic absorption of lidocaine" with (single-dose) product use. Because of the product's expected cost, it is unlikely that multiple administrations will occur during a single session (to the same, or to different skin sites). Therefore, systemic lidocaine levels are not expected, with clinical use of the approved product.

5.1 Lidocaine Pharmacokinetics

Absorption (Bioavailability)

Oral: \approx 35%

Lidocaine is absorbed from the gastrointestinal tract, enters the hepatic portal circulation, and is rapidly metabolized by the liver. Only 35% of the drug is absorbed and doses of 250 to 500 mg in adults result in subtherapeutic plasma concentrations (for arrhythmia treatment). However, oral absorption can produce therapeutic and even toxic plasma levels.

Intramuscular: "Adequate"

Adequate local anesthetic and systemic levels occur if injected into vascular muscle sites (e.g., deltoid muscle is preferable to the gluteus or vastus lateralis), and in the presence of adequate blood circulation to that site.

Epidural: "Extensive"

In one study, during cesarean section, a 5-cc epidural infusion of lidocaine 2% with epinephrine 1:200,000 has elicited a mean peak maternal arterial lidocaine concentration of 6.4 μ /mL at 31 minutes. The ratio of umbilical venous to maternal arterial levels was 0.43.

Topical: \approx 3%

With lidocaine 5% patch, about 3% of the dose is absorbed. Systemic absorption is related to the duration of application, and the surface area of application. With 3 patches (2100 mg), worn on the back (420 cm²) for 12 hours, mean peak lidocaine levels were about 0.13 μ /mL (Lidoderm^(R)).

In a study in 20 healthy volunteers, four 5% lidocaine patches were applied for 18-hours daily, for three days. Lidocaine plasma levels increased with time, reaching C_{max} toward the end of each dosing interval, and then declined rapidly to minimum levels (C_{min}). Mean C_{max} ranged from 145.1 ng/mL on Day 1 to 153.8 ng/mL on Day 3. These concentrations are \approx 10% of the therapeutic concentration required for the treatment of cardiac arrhythmias.

Distribution

Protein Binding is 33% to 80%, dependent upon both plasma drug and alpha-1-acid glycoprotein concentrations. At concentrations of 1 to 4 µ/mL of free base, lidocaine is 60% to 80% protein bound.

Tissue distribution is extensive. Lidocaine is distributed initially into highly-perfused tissues (i.e., kidneys, lungs, liver, and heart). Within 30 seconds, 70% of the injected drug has entered these highly perfused tissues with less than 1% metabolized. Lidocaine is also distributed into fat tissue.

Distribution half-life is 15 to 30 minutes. Distribution half-life of monoethylglycinexylidide (MEGX) ranges from 4 to 48 minutes. Volume of distribution is 1.7 L/kg in normal patients and 1 L/kg in patients with heart failure.

Metabolism

Approximately 90% of a lidocaine dose is metabolized via de-ethylation in the liver. CYP1A2 is the primary enzyme responsible for lidocaine metabolism, via oxidative de-ethylation and 3-hydroxylation. CYP3A4 appears to have a minor role in the biotransformation of lidocaine.

Monoethylglycinexylidide (MEGX) is similar in pharmacology and toxicity to lidocaine, but is less potent. MEGX is further metabolized to xylidine and N-ethylglycine. Although all the pharmacological effects of MEGX are not yet clearly elucidated, MEGX does possess convulsant activity in rats.

Glycinexylidide is similar in pharmacology and toxicity to lidocaine, but is less potent. Although all the pharmacological effects of glycinexylidide are not yet clearly elucidated, glycinexylidide does produce central nervous system toxicity (i.e., headache, seizures).

Excretion

Renal excretion is approximately 90%, in the form of metabolites. Less than 10% of the drug is excreted unchanged. Urinary excretion of unchanged drug is partly dependent on urinary pH. Urine acidification is reported to result in a larger fraction excreted in the urine.

Elimination half-life of the parent compound is 1.5 to 2 hours, in the absence of hepatic diseases or congestive heart failure. Elimination half-life of MEGX is 1 to 6 hours. Elimination half-life of glycinexylidide (GX) is 1 hour.

5.2 Pharmacodynamics

Factors that influence systemic absorption of locally *injected* lidocaine include the speed and site of injection, dose and concentration of lidocaine, and presence or absence of a vasoconstrictor such as epinephrine. A linear relationship between dosage and plasma lidocaine level exists. In general, higher plasma levels are achieved with *injection* of large volumes or high concentrations. The vascularity at the site of injection can significantly alter plasma levels. In areas of high vascularity the rate of absorption increases and produces high plasma levels of lidocaine. Epinephrine increases the intensity and duration of action of locally administered lidocaine and appreciably lowers plasma levels from all injection sites.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication (Local Analgesia Prior to Venipuncture or IV Cannulation)

Anesiva proposes the following *Indication and Usage* statement:

Zingo™ is a sterile, single-use, needle-free powder lidocaine delivery system (containing 0.5 mg lidocaine hydrochloride monohydrate) indicated for use on intact skin to provide local analgesia prior to venipuncture or intravenous cannulation.

Important Limitations:

- For use on intact skin only
- For external use only

6.1.1 Methods

The efficacy review focused on data from the two controlled final-device trials (3-003-1 and 3-004-1). Data from the five late-device (ND5.3) controlled trials were also reviewed. These studies are listed in Table 6-1. Primary and selected secondary analyses were confirmed by FDA's statistical review team.

Table 6-1: Studies Utilizing the ND5.3 and ND5.3A Devices Reviewed for Efficacy Findings

| Study | 1-100-1 | 1-102-1 | 4-401-1 | 4-400-1 | 2-002-1 | 3-003-1 | 3-004-1 |
|-------------------|--------------------|-------------------|--------------------|-------------------|-------------------|-------------------|-------------------|
| Population | Adult | Adult | Pediatric | Pediatric | Pediatric | Pediatric | Pediatric |
| Objective | Dose-ranging | Dose-ranging | Dose-ranging | Dose-ranging | Phase-3 | Phase-3 | Phase-3 |
| Device Used | ND5.3 | ND5.3 | ND5.3 | ND5.3 | ND5.3 | ND5.3A | ND5.3A |
| Pain Model | VP | VP | VP | VP | VP | VP/IV | VP/IV |
| Body Site | ACF | BOH | ACF | BOH | BOH | BOH/ACF | BOH/ACF |
| Number | 272 | 183 | 145 | 195 | 307 | 579 | 535 |
| Design | DB-XO | DB-XO | DB-PG | DB-PG | DB-PG | DB-PG | DB-PG |
| RX Sessions | 2* | 2* | 1 | 1 | 1 | 1 | 1 |
| Dose/ Pressure | 0.25 mg/ 20 bar | 0.5 mg/ 20 bar | 0.25 mg/ 20 bar | 0.5 mg/ 20 bar | 0.5 mg/ 20 bar | 0.5 mg/ 21 bar | 0.5 mg/ 21 bar |
| | 0.5 mg/ 20 bar | 0.5 mg/ 40 bar | 0.5 mg/ 20 bar | 0.5 mg/ 40 bar | 20 bar/ PBO | 21 bar/ PBO | 21 bar/ PBO |
| | 0.5 mg/ 40 bar | 20 bar/ PBO | 20 bar/ PBO | 20 bar/ PBO | | | |
| | 20 bar/ PBO | 40 bar/ PBO | | 40 bar/ PBO | | | |
| | 40 bar/ PBO | | | | | | |

(VP) venipuncture

(IV) IV cannulation

(ACF) antecubital fossa (BOH) back-of-hand

* Washout ≥ 6-days

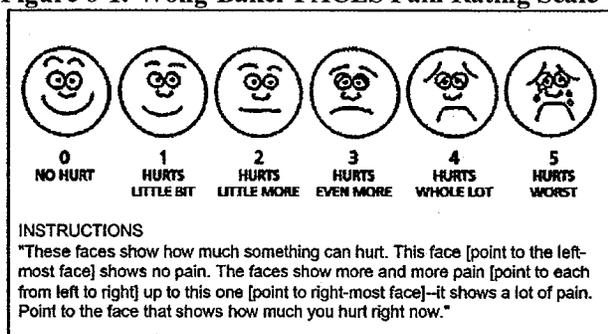
Source: Clinical reviewer

6.1.2 General Discussion of Endpoints

The primary efficacy measure in all late-device trials was subjects' assessment of pain, caused by venipuncture or intravenous cannulation, one to three minutes after study drug administration. The primary efficacy measurement instrument in the two final device studies, as well as in two of the other late-device trials, was an applicant-constructed, non-validated hybrid of two similar FACES scales.

Anesiva's "Modified Wong-Baker-FACES" pain rating scale is shown in Figure 6-1. The WB-FACES is a six-point scale anchored at zero ("No Hurt") and five ("Hurts Worst"). The pictures and their corresponding numerical values were unchanged from the original, validated instrument.

Figure 6-1: Wong-Baker FACES Pain Rating Scale



Instructions to subjects were modified, however, from those in the original instrument:

"Explain to the child that each face is for a person who feels happy because he has no pain (hurt) or sad because he has some or a lot of pain. Face 0 is very happy because he doesn't hurt at all. Face 1 hurts just a little bit. Face 2 hurts a little more. Face 3 hurts even more. Face 4 hurts a whole lot, but Face 5 hurts as much as you can imagine, although you don't have to be crying to feel this bad. Ask child to choose the face that best describes how he/she is feeling."

The instrument used during product development substituted instructions from the Faces Pain Scale-Revised, as described and validated by Hicks.

"These faces show how much something can hurt. This face [point to the left-most face] shows no pain. The faces show more and more pain [point to each from left to right] up to this one [point to right-most face]—it shows very much pain. Point to the face that shows how much you hurt right now."

The SEALD review concludes that the content validity of the modified instrument, with the altered instructions, has not been substantiated, because the new instructions were not shown to be appropriate and understandable for the target population. Anesiva's justification (for instrument modification) is primarily upon the opinion that children do not pay attention to verbatim verbal instructions. SEALD considers this argument to be inadequate.

The new instructions, taken from a very similar scale (which has also been validated), are themselves substantively and conceptually similar to the original. While not ideal, the modified instrument is acceptable. Furthermore, use of an instrument lacking content validity would most likely bias against supportive efficacy findings, hindering the applicant's ability to demonstrate product efficacy.

In Phase-3 studies, subjects and parent VAS scores were obtained, in addition to the modified WB-FACES scores. Procedure success was also recorded.

Table 6-2: Instruments Used to Assess Efficacy in Pediatric Studies (Shaded = Primary Endpoint)

| Study | Wong-Baker FACES ^a | FPS-R | Subject VAS | Parent VAS | Procedure Success |
|-----------|-------------------------------|------------|-------------|------------|-------------------|
| 3-003-1 | All subjects | -- | 8-18 years | All | All |
| 3-004-1 | All subjects | -- | 8-18 years | All | All |
| 2-002-1 | 3-12 years | -- | 8-18 years | All | -- |
| 4-401-001 | -- | 3-12 years | 8-18 years | -- | -- |
| 4-400-001 | 3-12 years | -- | 8-18 years | -- | -- |

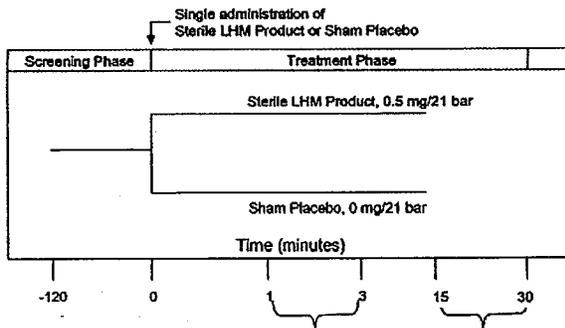
^a The modified Wong-Baker FACES scale utilized instructions that were modified from the originally described scale.

6.1.3 Study Design

6.1.3.1 Design of Final-Device Trials (ND5.3A) (3-003-1 and 3-004-1)

Both final-device trials used the same study design, patient population, entry criteria, treatments and efficacy endpoints. Both were double-blind, placebo-controlled, parallel-group studies in pediatric subjects, as shown in Figure 6-2. Subjects were treated once, either with active-drug or with placebo.

Figure 6-2: Study Design of Final-Device, Controlled Trials



The primary efficacy measure was subjects' assessment of pain, from venipuncture or peripheral IV cannulation performed one to three minutes after drug administration, measured using the applicant-modified Wong-Baker FACES scale, anchored at 0 for "no hurt" and 5 for "hurts worst" for all ages.

6.1.3.2 Design of Late-Device (ND5.3) Controlled Trials

Like the ND5.3A trials, the ND5.3 pediatric trials were double-blind, placebo-controlled, parallel-group studies. Subjects were treated once, with active-drug or with placebo. Two of these three trials included additional dose or pressure arms, as shown in Table 6-1 on page-17.

Adult Studies 1-100-1 and 1-102-1 were double-blind, placebo-controlled, within-subject, two-period crossover trials. Subjects were each treated once with active drug, and once with placebo. Study 1-100-1 included three active and two placebo arms, while Study 1-102-1 included two active and two placebo arms, as shown in Table 6-1.

6.1.4 Efficacy Findings

Efficacy analyses conducted in the late-device, pediatric trials are summarized in Table 6-3

Table 6-3: Applicant Efficacy Analyses by Pediatric Study

| Study | Subject FACES | Subject VAS | Parent VAS | Success Yes / No | Responder WB | Responder WB=0 or 1 | Responder VAS≤ 15 | Severe WB=5 |
|-----------|--|---|---------------|---------------------|-----------------|------------------------|----------------------|----------------|
| 3-003-1 | 3-18 y combined ^a | 3-18 y combined ^a | X | X ^b | X | X ^c | X ^c | X ^c |
| 3-004-1 | 3-18 y combined ^a | 3-18 y combined ^a | X | X ^b | X | X ^c | X ^c | X ^c |
| 2-002-001 | 3-7 y ^a ; 8-12 y ^a ; 3-12 comb ^b | 8-12 y; 13-18 y; 8-18 comb ^b | X | ND | X ^c | X ^c | X ^c | X ^c |
| 4-401-001 | 3-18 y combined ^{a, b} 3-7 y (FPS-R) 8-12 y (VAS); 8-12 y (FPS-R) 13-18 y (VAS) | | ND | ND | ND | ND | X ^c | ND |
| 4-400-001 | 3-18 y combined ^{a, b} 3-7 y (W-B) 8-12 y (VAS); 8-12 y (W-B) 13-18 y (VAS) | | ND | ND | X | X ^c | X ^c | X ^c |

^a Primary endpoint ^b Different pain scales combined, Glass' Delta method ^c Not prospectively specified
Source: Integrated Efficacy Summary, Table-4, page-14

6.1.4.1 Primary Efficacy Results

The results of the primary analyses (ITT) for Studies 3-003-1 and 3-004-1 are shown below.

Table 6-4: Final Device Studies, Modified Wong-Baker FACES Score (ITT)

| | <u>Study 3-003-1</u> | | <u>Study 3-004-1</u> | |
|-------------------------|----------------------|--------------------|----------------------|--------------------|
| | LHM (N= 92) | Placebo (N=287) | LHM (N=269) | Placebo (N=266) |
| Adjusted Mean, LSM | 1.77 | 2.10 | 1.38 | 1.77 |
| Standard Error of LSM | 0.09 | 0.09 | 0.09 | 0.09 |
| Difference in LSMs (SE) | -0.33 (0.13) | | -0.39 (0.13) | |
| p-value | 0.011 | | 0.003 | |
| 95% Confidence Limits | -0.58, -0.08 | | -0.65, -0.13 | |

Source: Study 3-003-1 Tables 11.1.10 and 5.1.1B, Study 3-004-1 Tables 11.1.10 and 5.1.1B in Section-14

In both studies, treatment with active drug resulted in statistically significantly less pain, from venipuncture or IV cannulation, compared with placebo. Effect sizes were rather small, however.

6.1.4.2 Key Secondary Efficacy Results

Overall, the secondary efficacy findings (Subject VAS and parent VAS) from Studies 3-003-1 and 3-004-1 confirm the primary findings. In Study 3-003-1 subjects ages eight through eighteen reported (statistically significantly) less procedure-related pain, as measured by 100-mm VAS, when pre-treated with LHM, compared with placebo (Table 10-11 in Section 10.1.13). Parents also perceived their children to experience less procedure-related pain, as assessed by 100-mm VAS, when pre-treated with LHM, compared with placebo (Table 10-12). The 3-004-1 Subject-rated VAS findings (in 8 to 18 year-olds) do not reach statistical significance, however.

Table 6-5: Final Device Studies, Subject VAS (Ages 8 to 18)

| ITT Population | 3-003-1 | | 3-004-1 | |
|-------------------------|----------------|--------------------|----------------|--------------------|
| | LHM (N=206) | Placebo (N=200) | LHM (N=183) | Placebo (N=185) |
| Adjusted Mean, LSM | 22.62 | 31.97 | 16.58 | 21.47 |
| Standard Error of LSM | 1.80 | 1.82 | 1.80 | 1.78 |
| Difference in LSMs (SE) | -9.35 (2.56) | | -4.89 (2.53) | |
| p-value | <0.001 | | =0.054 | |
| 95% Confidence Limits | -14.4, -4.31 | | -9.87, 0.09 | |

Source: Study 3-003-1 report Tables 11.1.11 and 5.2.1 Study 3-004-1 Tables 11.1.10 and 5.1.1B

Table 6-6: Final Device Studies, Parent VAS Assessment of Child's Pain, Ages 3-18

| ITT Population | 3-003-1 | | 3-004-1 | |
|-------------------------|----------------|--------------------|----------------|--------------------|
| | LHM (N=292) | Placebo (N=287) | LHM (N=269) | Placebo (N=266) |
| Adjusted Mean, LSM | 21.69 | 28.92 | 16.66 | 22.97 |
| Standard Error of LSM | 1.54 | 1.54 | 1.44 | 1.45 |
| Difference in LSMs (SE) | -7.24 (2.18) | | -6.31 (2.04) | |
| p-value | ≈0.001 | | ≈0.002 | |
| 95% Confidence Limits | -11.5, -2.96 | | -10.3, -2.29 | |

Source: CSR 3-003-1 Table 5.4.1B, Section-14, CSR 3-004-1 Table-5.4.1, Section 14

6.1.4.3 Dose-Response Evaluation (See Section 8.1)

In addition to pediatric dose ranging Studies 4-400-1 and 4-401-, the two adult late-device controlled studies varied dose/pressure, and time-to-venipuncture. These data combined with those from early-device studies show that:

- No apparent efficacy differences between 0.50-mg and 1.0-mg lidocaine doses
- Possibly increased efficacy at lidocaine 3.0-mg, but more frequent AEs and abnormal skin findings
- No efficacy difference over the 20-bar to 30-bar range
- Possibly decreased efficacy at 40-bar and above, with increases in AEs and abnormal skin findings

6.1.4.4 Time to Onset and Duration of Analgesia

The time-to-venipuncture findings (from the two adult ND5.3 studies) show greatest efficacy at one and three minutes, with waning efficacy by ten-minutes post-treatment. (Tables 6-7 and 6-8).

Table 6-7: Study 1-102-1, Efficacy by Time-to-Venipuncture (Anesiva Efficacy Evaluable Population)

| Treatment Group | N | Mean SE | Median | Range | 95% CI | P-Value |
|-------------------------------|----|-------------|--------|---------|----------------|---------|
| 0.50-mg/20-bar vs. PBO | | | | | | |
| Total | 79 | -2.7 ± 3.0 | -3.0 | -54, 77 | (-8.7, +3.2) | 0.364 |
| 1-min | 20 | -12.7 ± 4.7 | -7.0 | -54, 23 | (-22.4, -3.0) | 0.013 |
| 3-min | 19 | 4.6 ± 7.5 | +3.0 | -40, 77 | (-11.0, +20.3) | 0.542 |
| 5-min | 20 | -5.1 ± 4.9 | -3.0 | -46, 35 | (-15.3, +5.2) | 0.315 |
| 10-min | 20 | 2.5 ± 6.4 | +2.5 | -42, 70 | (-11.0, +16.0) | 0.702 |
| 0.50-mg/40-bar vs. PBO | | | | | | |
| Total | 80 | -5.7 ± 2.7 | -3.5 | -72, 48 | (-11.2, -0.2) | 0.043 |
| 1-min | 20 | -11.8 ± 6.3 | -4.0 | -72, 44 | (-25.1, +1.5) | 0.079 |
| 3-min | 20 | -2.3 ± 5.0 | -2.0 | -48, 39 | (-12.8, +8.2) | 0.653 |
| 5-min | 20 | -4.6 ± 5.1 | ±0.0 | -67, 28 | (-15.4, +6.2) | 0.383 |
| 10-min | 20 | -4.1 ± 5.5 | -9.5 | -51, 48 | (-15.7, +7.5) | 0.468 |

Source: Table 14.1, 1-102-001 CSR

Table 6-8: Study 1-100-1, VAS Score after Venipuncture, by Time to Venipuncture; Treatment Group Difference versus Placebo (Mean ± SE / (Range))

| Treatment Group | N | 1-Min | 3-Min | 5-Min | 10-Min | 15-Min | 20-Min |
|---------------------------|------|-------------------------------|-------------------------------|-------------------------------|-----------------------------|-----------------------------|------------------------------|
| Active 0.25mg/20-bar (1R) | (10) | -7.8 ± 5.9 (-21.2, 5.6) | -5.7 ± 13.5 (-36.3, 24.9) | -17.7 ± 9.8 (-39.9, 4.5) | -10.5 ± 6.7 (-25.7, 4.7) | +4.5 ± 7.4 (-12.3, 21.3) | -9.7 ± 11.1 (-34.9, 15.5) |
| Active 0.50mg/20-bar (2R) | (10) | -17.7 ± 13.3 (-41.3, 5.9) | -17.1 ± 13.3 (-47.1, 12.9) | -15.5 ± 8.1 (-33.7, 2.7) | +0.0 ± 6.4 (-14.5, 14.5) | -1.3 ± 7.8 (-18.6, 16.0) | -15.0 ± 7.4 (-31.8, 1.8) |
| Active 0.50mg/40-bar (3R) | (10) | -13.4 ± 4.8* (-24.3, -0.3) | -23.3 ± 9.1* (-44.0, -2.6) | -15.7 ± 9.9 (-38.1, 6.7) | +3.3 ± 4.6 (-7.1, 13.7) | +3.3 ± 4.6 (-27.7, 4.1) | -10.2 ± 7.2 (-26.6, 6.2) |
| Groups 1R and 2R combined | (20) | -12.8 ± 5.9 (-25.2, -0.3) | -11.4 ± 9.3 (-30.9, 8.1) | -16.6 ± 6.2* (-29.5, -3.7) | -5.3 ± 4.7 (-15.0, 4.5) | -5.3 ± 4.7 (-9.6, 12.5) | -12.4 ± 6.5 (-26.1, 1.4) |

Source: Extracted from Table 10-42 on page-117

6.1.5 Clinical Microbiology

This section is not applicable to this review.

6.1.6 Efficacy Conclusions

The primary efficacy data from the two final-device, controlled trials provide support for Anesiva's efficacy claim; Zingo™ provides local analgesia when administered on intact skin. Secondary efficacy data from these trials are generally supportive, as are data from the Phase-2 dose-ranging studies.

Data from the two controlled adult (late-device) studies suggest maximum treatment effect one to three minutes after treatment, with efficacy waning within ten minutes of dosing.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

No deaths were reported during development or study follow-up, in active or comparator-treated subjects.

7.1.2 Other Serious Adverse Events

Early Device Studies

A total of five SAEs (in four subjects) were reported in the 14 early device studies, none plausibly treatment-related. Table 7-1 on page-24 summarizes pertinent AE and treatment details.

- Two were in Study DPJ-01-002 (which utilized the initial ND1 prototype device), a within-subject crossover study, in post-operative, adult heart, lung and heart-lung transplant outpatients undergoing venipuncture at their periodic follow-up care visits. Each of the 40-subjects received two study treatments, one to each ACF, less than 15-minutes apart; a single LHM treatment (3-mg at 40-bar) and a single mannitol treatment (40-bar). Both were systemic SAEs, thus attribution of causality to active or mannitol treatment would be difficult given the close temporal proximity of administration. Neither SAE seems plausibly related to study treatment, however.
 - Subject DPJ-01-002-16, a 57 year-old female on chronic immunosuppressive therapy, with a history of Eisenmenger's Syndrome and asthma, was noted to have "decreased lung function" on routine PFTs two-hours after study treatment (compared with months prior). "A shadow" was seen on chest radiography. Bronchoscopy "... revealed an infection which was treated with antibiotics." The patient, hospitalized for nearly one month, recovered by discharge.
 - Subject DPJ-01-002-17, a 56 year-old male with a history of ischemic cardiomyopathy (on chronic immunosuppressive therapy), was noted to have "decreased lung function" on routine PFTs two-hours after study treatment (compared with months prior). Chest radiograph findings were consistent with infectious pneumonia. He was hospitalized for one-week (recovered).
- Three were in Study 031091 (initial ND1 prototype), a double-blind, mannitol-device controlled, parallel-group study, in chronically ill pediatric (in and out) patients, ages 4 to 14. Each subject received a single study treatment, to the ACF or the BOH. Device pressures of 30-bar and 40-bar, and particle sizes of <38- μ and 38- μ to 53- μ were studied. Follow-up was to one-month post-RX.
 - Subject 031091-0019, a 14 year-old male with ulcerative colitis (several flares yearly) on chronic immunosuppressive therapy, experienced two SAEs after treatment with the lidocaine 3.0-mg/30-bar device; ulcerative colitis flare 11-days post-RX lasting 15-days, and "bacterial chest infection" 28-days post-RX, lasting four-days.
 - Subject 031091-0031, a 13-year-old Type-1 diabetic, had an episode of DKA >25-days after placebo treatment (resolved within 24-hours).

Late Device Studies

Eight subjects in the nine ND5.3A and ND5.3 studies experienced treatment-emergent SAEs, none of which seem to be plausibly related to study treatment. Five subjects randomized to active LHM experienced five-SAEs, while three patients randomized to placebo experienced SAEs (three concurrent AEs in one subject, all coded as serious). These SAEs are listed in Table 7-2 below, with additional information beginning on page26

Table 7-1: Serious Adverse Events, Early Device Studies (WHO-ART Coding)

| Study / PID / Age/ Sex | System Organ Class | Preferred Term | Verbatim Term | RX | Onset | Stop |
|--|---------------------------------|-------------------------------|--|----|---------------------|-----------|
| <u>LHM 3.0-mg/40-bar & Mannitol/40-bar (X-Over)</u> | | | | | | |
| DPJ-01-002 / 016 / 57F | Respiratory System Disorder | Respiratory Disorder | Shadow on CXR, Infection PFTs worsened | | | |
| DPJ-01-002 / 017 / 58M | Respiratory System Disorder | Respiratory Disorder | Shadow on CXR, Infection | | | |
| <u>LHM 3.0-mg/30-bar</u> | | | | | | |
| 031091 / 019 / 14M | Gastrointestin. System Disorder | Colitis Ulcerative Aggravated | Exacerbation of Ulcerative Colitis | | 27-Apr-99 09-May-99 | 24-May-99 |
| 031091 / 019 / 14M | Resistance Mechanism Disorder | Infection Bacterial* | Chest Infection | | 27-Apr-99 26-May-99 | 30-May-99 |
| <u>Placebo/30-bar</u> | | | | | | |
| 031091 / 031 / 13M | Metabolic/Nutritional Disorder | Ketosis | Diabetic Ketosis | | 20-Aug-99 16-Sep-99 | 17-Sep-99 |

WHO-ART coding Source: Clinical reviewer from Amendment-007, table-20.1, page-4 and clinical study reports for Studies DPJ-01-002 and 031091

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Table 7-2: Serious Adverse Events, Late Device Studies (MedDRA Version 7.0)

| Study / PID / Age/ Sex | System Organ Class | Preferred Term | Verbatim Term | RX | Onset | Stop |
|----------------------------|--------------------------------|-----------------------|--------------------------|----|---------------------|-----------|
| LHM 0.50-mg/20-bar | | | | | | |
| 1-100-001 / 0162 / 43F | General D/O, Site Conditions | Chest pain | Chest pain | | | ↓ |
| 3-003-1 / 3058 / 17M | Immune System Disorders | Anaphylactic reaction | Anaphyl. RXN to contra. | | | ↓ |
| 4-400-001 / 0360 / 13F | Surgical/Medical Procedures | Hospitalization | Hospitalization | | | ↓ |
| LHM 0.25-mg /20-bar | | | | | | |
| 1-100-001 / 0069 / 23F | Injury, Poisoning, Proc. Comp. | Spinal fracture NOS | Fracture of C2, C3, C4 | | 23-Sep-02 25-Sep-02 | Ongoing |
| 4-401-001 / 0341 / 14M | Surgical/Medical Procedures | Hospitalization | Hospitalization | | | ↓ |
| Placebo | | | | | | |
| 3-003-1 / 3087 / 18M | Respiratory, thoracic | Laryngospasm | Post-extub. laryngospasm | | 15-Mar-05 15-Mar-05 | 15-Mar-05 |
| 3-003-1 / 3103 / 15F | Blood and lymphatic | Leukocytosis | Leukocytosis | | | ↓ |
| 3-003-1 / 3103 / 15F | Metabolism/ nutrition | Dehydration | Dehydration | | | ↓ |
| 3-003-1 / 3103 / 15F | Nervous System | Migraine NOS | Migraine | | | ↓ |
| 4-400-001 / 0157 / 6M | Surgical/Medical Procedures | Hospitalization | Hospitalization | | | ↓ Ongoing |

Source: Clinical reviewer from ISS Table-20, individual clinical study reports and dataset aaccess1.xpt

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SAEs in Late-Device Trials (ND5.3 and ND5.3A Devices)

Three SAEs were coded as “Hospitalization,” none of which are plausibly treatment-related:

- 4-401-001-0341 (LHM 0.5-mg / 20-bar); Verbatim = “Elevated level of Prograf”
This 14-year-old male subject had been on the immunosuppressant drug tacrolimus since liver transplantation. He underwent routine follow-up laboratory work (including drug levels) – the reason for clinical trial recruitment – on 13-Jan-2004, and was noted to have an elevated tacrolimus level. **b(6)**

- 4-400-001-0360 (LHM 0.5-mg / 20-bar); Verbatim = “Suspicion of graft rejection”
This 13-year-old female subject had undergone kidney transplantation on [redacted]. She underwent routine outpatient follow-up laboratory testing - the reason for clinical trial recruitment [redacted] and was noted to have values suggestive of possible organ rejection, for which she was hospitalized. **b(6)**

- 4-400-001-0157 (Placebo); Verbatim = “Exacerbation of nephrotic syndrome”
This 6-year-old male subject with a history of nephrotic syndrome since infancy (etiology not described in application) underwent follow-up venipuncture - the reason for clinical trial recruitment – [redacted]. He was admitted to the hospital that day because of worsening renal function and electrolyte disturbances. **b(6)**

Five additional subjects experienced SAEs, none of which seem to be plausibly treatment related.

- 1-100-001-0162 (LHM 0.5-mg / 20-bar); Verbatim = “Chest pain”
This 43-year-old female subject’s past medical history is not described, but she took no prescription or OTC medications. Her study participation was voluntary (for monetary remuneration). She experienced chest pain six-days after administration of the first of two study treatments (within-subject crossover trial). She was hospitalized overnight, and discharged with a diagnosis of “chest pain.” No additional details are provided.

- 3-003-1-3058 (LHM 0.5-mg / 20-bar); Verbatim = “Anaphylactic allergic reaction to contrast”
This 17-year-old male subject had a PMH significant for pancreatitis and previous allergic reaction to ionic contrast media. At 12:46 PM he received study treatment to the left BOH, prior to IV cannulation for medication and contrast administration. He was pre-medicated with oral diphenhydramine and prednisone. Approximately 45-minutes later, contrast was administered both orally and intravenously. Soon afterwards (1:39 PM) he developed erythema, hives, and vomiting that were reported to be of “moderate” severity. He was transferred to the emergency department where he was noted to have erythema, flushed inflamed skin, and pruritus of the entire body, but no wheezing or difficulty breathing. He was diagnosed with “anaphylactic reaction,” admitted, treated with diphenhydramine, prednisone, ranitidine, and ondansetron, and then discharged the same day.

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- 1-100-001-0069 (LHM 0.5-mg / 20-bar); Verbatim = "Fracture of C2, C3, C4"
Subject 1-100-0010069, a 23-year-old female without significant PMH, experienced cervical spinal fractures from a car accident 2-days after the first of two study treatment sessions (within-subject crossover). Her only medication was Lunelle® (Estrogen/progestin, once-monthly contraceptive injection). She was treated surgically on the day following the accident _____ . She was still recuperating as of database lock, thus her SAE was considered to be ongoing.
- 3-003-1-3087 (Placebo); Verbatim = "After extubation laryngospasm developed"
This 18-year-old male had a PMH significant for pilonidal and ganglion cysts. He had surgery for excision of a pilonidal cyst, receiving general anesthesia. He received study drug (placebo) shortly prior to an initial attempt at left BOH IV cannulation. The cannulation attempt was unsuccessful and the subject was discontinued from the study. The second attempt was successful.

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Following extubation the subject developed an SAE of "moderate laryngospasm," during which pulse oximetry decreased to 70% (duration not stated). He responded well to treatment with positive pressure ventilation. The concomitant medications, all perioperative only, included lidocaine, thiopental, sevoflurane, thrombin, neotracin, nitrous oxide, propofol, rocuronim, and fentanyl. The event resolved on the same day without sequelae.

- 3-003-1-3103 (Placebo); Verbatim = "After extubation laryngospasm developed"
This 15-year-old female had a PMH significant for "...migraine headaches, menstrual cycle irregularities, attention deficit disorder, and sore throat." She presented to an outpatient primary care clinic complaining of "... a migraine headache, nausea and dehydration" that began several hours prior. Study drug was administered to the left BOH for IV cannulation, for fluid and medication administration. Laboratory work revealed leukocytosis (WBC≈ 23K with granulocytes 88%, lymphocytes 6%, and monocytes 6%), and hypovolemia with metabolic acidosis (CO₂=17).

She received intravenous fluids (volume and type not specified). "A CT scan was performed with normal results." (Site not specified) She was admitted to the hospital overnight. The narrative states, "Concomitant medications included Mylanta, phenol, cyproheptadine, ethinyl estradiol/drospirenone, ondansetron hydrochloride, metoclopramide, Reglan, and dihydroergotamine," but does not indicate which were administered only acutely, while hospitalized. All events resolved the following day and the subject was discharged.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Nine of the fourteen early-device trials, and seven of the nine late-device trials were single-dose studies, in which dropout could only occur after (same day) screening, but prior to treatment, or, shortly after treatment during the brief follow-up assessment period (one to three hours in most trials). Late-device Studies 1-100-001 and 1-102-001 called for two treatment sessions, approximately one-week apart.

Phase-1 (Early Device) Studies

The applicant's integrated safety summary (Amendment #007, 6/25/07) reported no cases of subject dropout prior to study completion. My review of the individual study reports, however, identified a skin reaction for which Study 031091 was terminated. Subject 107 in Study 031091, a ten year-old

female with recent meningitis (organism not named), who, after study treatment, experienced Grade-4 erythema with subsequent skin sloughing.

Phase-2/3 (Late-Device) Studies

Of 455 subjects enrolled in Studies 1-100-001 and 1-102-001, 59 discontinued prior to completion of both study treatment sessions. A summary of subject disposition appears in Table 7-3 below. Most withdrawals were due to failed initial venipuncture attempts, or to protocol deviations.

Three discontinuations were possibly AE-related, seven (all in 1-102-001) were attributed to withdrawal of consent, and the remaining 49 were categorized as “administrative discontinuations.” The three AE-related dropouts are discussed in Section 7.1.3.2 below (along with one additional subject from pediatric Study 4-401-001).

“Administrative discontinuations” were mostly failed venipuncture attempts (N=34/49). The two studies used different disposition categorization schemes, though. Ten subjects were discontinued from 1-100-001 for “noncompliance” or for “failure to comply with protocol,” while only one was discontinued from 1-102-001 for “study treatment not per protocol.” Study 1-102-001 utilized a withdrawal of consent category (1-100-001 did not).

Table 7-3: Disposition in Late-Device, Within-Subject (Active ↔ Placebo) Crossover Studies* (N=455)

| Active Treatment → ↓Disposition↓ | 1-100-001 (N=272) | | | 1-102-001 (N=183) | |
|-------------------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| | 20-bar/ 0.25-mg | 20-bar/ 0.50-mg | 40-bar/ 0.50-mg | 20-bar/ 0.50-mg | 40-bar/ 0.50-mg |
| Randomized | 90 | 96 | 86 | 91 | 96 |
| Treated-Completed | 80 (89.0) | 80 (83.3) | 80 (93.0) | 80 (87.9) | 80 (83.3) |
| Treated-Discontinued | 10 (11.1) | 16 (16.7) | 6 (7.0) | 11 (12.1) | 16 (16.7) |
| Reason for Discontinuation | | | | | |
| Adverse Event | 2 (2.2) | 1 (1.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Withdrew Consent | NA | NA | NA | 2 (2.2) | 5 (5.4) |
| Administrative | 8 (8.9) | 15 (15.6) | 6 (7.0) | 9 (9.9) | 7 (7.6) |
| Failed venipuncture attempt | 6 (6.7) | 11 (11.4) | 2 (2.3) | 9 (9.9) | 6 (6.5) |
| Noncompliance | 2 (2.2) | 2 (2.1) | 3 (3.5) | NA | NA |
| Failed to Comply with Protocol | 0 (0.0) | 2 (2.1) | 1 (1.2) | NA | NA |
| Study Treatment not per Protocol | 0 (0.0) | 2 (2.1) | 1 (1.2) | 0 (0.0) | 1 (1.1) |

*Studies 1-100-001 and 1-102-001: In both, there were two single-dose sessions, one active drug, the other placebo
Sources: 1-100-001 report Table 14.1 and data listings 16.2.5, 1-102-001 report Table 14.1 and data listing 16.2.16

The study report for Study 1-102-001 does not provide information about subjects’ reasons for consent withdrawal, but review of the data listings for these seven subjects shows that only one reported an adverse event. Subject 1-102-001-0205, a 52 year old healthy female volunteer with noncontributory PMH, reported right foot pain beginning the day after her first treatment session (0.50-mg/20-bar to BOH), and lasting for six-days.

Review of the data listings for subjects withdrawn due to noncompliance and failure to comply with the protocol shows that in each case, the investigator (or study staff) was responsible, not the subject

(i.e., inadequate collection of screening data, late discovery of failure to meet a study entry criterion, failure to record baseline skin assessments). Most of these cases are listed in protocol deviation summaries contained within the individual study reports.

7.1.3.2 Adverse events associated with dropouts

Phase-1 (Early Device) Studies

As noted above, no subject dropouts from early-device trials were identified.

Phase-2/3 (Late Device) Studies

Four subjects discontinued early, in the setting of adverse events. Seven of the nine late-device trials were single-dose studies, however, thus dropout during the brief trial would be unusual. Three of the four AE-related discontinuations occurred in Study 1-100-001, one of the two-session trials. The four discontinuations are listed in Table 7-4 below.

Review of these subjects' narrative reports and data listings shows that only the third and fourth (Subjects 1-100-001-0204 and 4-401-001-0136) may plausibly have been related to study treatment (placebo in both cases). The first two listed, both in active-drug-treated subjects, were also categorized as SAEs. These two subjects (1-100-001-0162 and 1-100-001-0069) are discussed on page 26 and on page 27 above. Neither of the first two listed seem plausibly related to study treatment.

Subject 1-100-001-204 was a 19-year-old male with no significant PMH (and no concomitant medications), whose skin assessments during the two-hours following treatment had been normal, except for Grade-1 treatment-site pruritus at 30-minutes (right ACF). He reported generalized urticaria two-days following placebo treatment, for which he was discontinued by the investigator, and treated with oral diphenhydramine (resolution < 2-days). Generalized urticaria reaction could, conceivably have been a type of dermatographia, resulting from dermal exposure to pressure alone. This seems exceedingly unlikely, however, given the subject's lack of allergic or atopic history.

Subject 4-401-001-0136 was a 3-year-old female with a PMH of hypercalciuria, recurrent urinary tract infections, and vesicoureteral reflux. She was treated with placebo (20-bar) prior to scheduled venipuncture. She "... experienced an attack of hysteria immediately after being treated." The event resolved the same day without pharmaceutical treatment, and with no apparent sequelae. This AE, though perhaps miscoded as conversion disorder, seems likely to have been related to study treatment.

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Table 7-4: Discontinuations due to Adverse Events, Late-Device (Phase-2/3) Studies

| Study / PID / Age/ Sex | System Organ Class | Preferred Term | Verbatim Term | RX | Onset | Stop |
|--------------------------|--------------------------------|-----------------------|------------------------|-----------|-----------|-----------|
| LHM 0.5mg/20 bar | | | | | | |
| 1-100-001 / 0162 / 43F | General D/O, Site Conditions | Chest pain | Chest pain | 1 | | 1 |
| LHM 0.25mg/20 bar | | | | | | |
| 1-100-001 / 0069 / 23F | Injury, Poisoning, Proc. Comp. | Spinal fracture NOS | Fracture of C2, C3, C4 | 23-Sep-02 | 25-Sep-02 | Ongoing |
| Placebo | | | | | | |
| 1-100-001 / 0204 / 19M | Skin and Subcutan. Tissue D/O | Urticaria generalized | Generalized urticaria | 24-Sep-02 | 26-Sep-02 | 27-Sep-02 |
| 4-401-001 / 0136 / 3F | Psychiatric Disorders | Conversion Disorder | Attack of hysteria | 01-Jul-03 | 01-Jul-03 | Ongoing |

Source: ISS Appendix Table-15 and data listing 16.3.

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7.1.3.3 Other significant adverse events

Phase-1 (Early Device) Studies

My review of the fourteen individual clinical study reports, and of the applicant's integrated safety summary (Amendment #007, 6/25/07) identified one noteworthy case not counted/ categorized as an SAE. This case, for which Study 031091 was terminated, was most likely treatment-related. Subject 107 in Study 031091, a ten year-old female with recent meningitis (organism not named), who, after study treatment, experienced Grade-4 erythema with subsequent skin sloughing. She recovered over the following week, though specific therapeutic measures are not described.

Phase-2/3 (Late Device) Studies

Anesiva categorized three AEs as "Other significant adverse events." Two of these, however, were AEs leading to discontinuation, discussed on page 29 (Subjects 1-100-001-204 and 4-401-001-0136, the 19 year-old male with generalized urticaria, and the 3 year-old with "conversion disorder," respectively). Anesiva categorized one additional AE as "significant," right arm cellulitis in a healthy 15 year-old female, described below.

My review of the adverse event datasets and line listings, and of the individual clinical study reports, uncovered no additional noteworthy AEs.

Subject 3-003-1-3086 was a 15-year-old Caucasian female treated with LHM (0.5-mg/21-bar, right BOH) via the final device formulation (ND5.3A). She underwent right retrocalcaneal exploration and debridement (for unstated purpose), under general anesthesia, for which peripheral IV was required. Post study treatment and postoperative skin assessments were all graded as 0 except for Grade-1 erythema reported 15 and 30 minutes post study drug administration. Three days following (outpatient) surgery she was seen by her primary care physician for right arm redness, and diagnosed with cellulitis... She was treated with oral Bactrim for 10-days (AE resolved).

Her "Concomitant medications included Marcaine® with epinephrine, midazolam, cefazolin sodium, Propacet®, sevoflurane, hydromorphone, Vicodin®, fentanyl, propofol, promethazine, ibuprofen, ethinyl estradiol/drospirenone, and dolasetron mesilate." The narrative does not state, however, which of these were administered peri or postoperatively, and which were chronic use medications.

7.1.4 Other Search Strategies

Skin-related findings were of particular interest during product development. Though (mostly) not classified as adverse events, skin reaction categorization and reporting are discussed in Section 7.1.5 below (Common Adverse Events).

7.1.5 Common Adverse Events

7.1.5.1 Eliciting AE and skin reaction data in the development program

The skin at treatment administration sites was "...rigorously and consistently assessed," before and after treatment, at protocol-specified time points. A scoring system consisting of four categories of potential skin changes was used; erythema, edema, pruritus, and hemorrhage/petechiae. Each category was graded on an ordinal scale, as shown in Table 7-5 below.

Table 7-5: Grading Scales for Assessment of Skin Changes (Late-Device Studies)

| Grade | Erythema | Edema | Pruritus | Hemorrhage/Petechiae |
|-------|---|--|-------------|---|
| 0 | No erythema | No edema | No pruritus | None |
| 1 | Very slight erythema (barely perceptible) | Very slight edema (barely perceptible) | Occasional | Up to 5 isolated petechiae |
| 2 | Well defined erythema | Slight edema (area edges well defined by raising) | Constant | Greater than 5 isolated petechiae |
| 3 | Moderate to severe erythema | Moderate edema (raised ≈ 1-mm) | N/A | Many petechiae, with some coalescence |
| 4 | Severe erythema (beet red) to slight eschar formation | Severe edema (raised > 1 mm, extending beyond exposure area) | N/A | Numerous petechiae ± pin-prick surface blood spots, or surface bleeding |
| 5 | N/A | N/A | N/A | Frank bleeding |

Source: ISS page-7, Table-1 and page-8, Table-2

The erythema and edema assessments utilized the Draize scale (Draize 1944), deemed acceptable in FDA/CDER, Guidance for Industry - Immunotoxicology Evaluation of Investigational New Drugs, 2002, and in draft document, Guidance for Industry - Skin Irritation and Sensitization Testing of Generic Transdermal Products, 1999.

Anesiva constructed the pruritus and petechiae scales early during LHM development. They were used consistently, though no validation research findings have been presented.

These data were tabulated and analyzed apart from (in addition to) the AE data. Skin findings meeting any of the following criteria were, however, coded and reported as AEs:

- Could not be adequately described using the protocol-specified skin site assessments for erythema, edema, pruritus and hemorrhage/petechiae (described below)
- Noted at a time point when skin site assessments were not scheduled
- Met SAE criteria

(Several investigators did, however, report pruritus adverse events.)

Erythema and edema scores ≥ 3 were tabulated by study population, device configuration and skin site. All itching and petechiae data were tabulated by study population, device configuration and skin site.

The time courses for post-treatment skin site findings are summarized for the two controlled, final-device pediatric studies (3-003-1 and 3-004-1) in Section 7.4.2.2 below.

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7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Overall, adverse event elicitation, coding, categorization and summary reporting were acceptable.

Adverse events were defined as “Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease ... whether or not considered related to the investigational product.” Early-device studies employed WHO-ART coding, while late-device studies used the Medical Dictionary for Regulatory Activities (MedDRA) Version 7.0.

Within-Subject Crossover Trials

In all trials, at each contact with the subject, the investigator or designee directly questioned about adverse events, and conducted a confirmatory examination where appropriate.

Treatment-emergent adverse event Preferred Terms were counted only once for each subject, in early-device trials. If the same PT occurred on multiple occasions in a single subject ($N \leq 5$), the AE of highest severity was counted in summary tables.

In single-session, within-subject crossover trials, adverse events that were clearly related to treatment administration site (e.g., microhemorrhage, purpura, pruritus) were attributed to the specific treatment at that anatomical site. General (systemic) AEs, however, such as nausea and headache, that were thought unrelated to the anatomic site of study treatment, were counted under both study treatments.

Both final-device studies utilized a parallel-group design, in which each subject received only one treatment; AEs in these trials were always attributed to only one treatment.

Skin Changes

Transient skin changes at the study drug administration site were not reported as adverse events, unless meeting one of the following criteria:

- Could not be adequately described using the protocol-specified skin site assessments for erythema, edema, pruritus and hemorrhage/petechiae
- Noted at a time point when skin site assessments were not scheduled
- Met SAE criteria

(Three cases each, however, of erythema and of pruritus, were coded by investigators as adverse events despite not meeting these criteria.)

Anesiva's adverse event summary tables, for the late-device trials, reported:

- For all events occurring in at least 0.5% of subjects in any treatment group
- For all treatment-related events (investigator attribution of treatment relatedness)
- For all treatment-related events by intensity (investigator attribution of treatment relatedness)

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7.1.5.3 Incidence of common adverse events

Early-Device Studies

Table 7-6 below summarizes AE incidence rates in the overall ND5.3A and ND5.3 studies (adult and pediatric), and from the controlled pediatric studies (3-003-1 and 3-004-1), by treatment group. In both populations similar proportions of active-treated and placebo-treated subjects experienced treatment-emergent AEs (TEAEs), and treatment-related TEAEs (by Anesiva's assessment).

Table 7-6: Safety Overview - Adverse Events in Early-Device Studies

| Number (%) of Subjects | 0.50-mg/ | >0.50-mg | >0.50-mg | Placebo | Placebo | Mannitol |
|------------------------|-------------|-----------------|-------------|-------------------|-----------|-----------|
| | 20-25 bar | 20-25 bar | >25 bar | 20-25 bar | >25 bar | >25 bar |
| | N=60 (%) | N=110 (%) | N=400 (%) | N=140 (%) | N=202 (%) | N=106 (%) |
| Any AE | 27 (45.0) | 73 (66.4) | 187 (46.8) | 58 (41.4) | 53 (26.2) | 62 (58.5) |
| Related, my assessment | (<25%) | (<30%) | (<30%) | (<20%) | (<15%) | (≈50%) |
| Related, per Anesiva | 12 (20.0) | 54 (49.1) | 150 (37.5) | 19 (13.6) | 21 (10.4) | 56 (52.8) |
| Severe AE | 1 (1.7) | 1 (0.9) | 2 (0.5) | 1 (0.7) | 1 (0.5) | 1 (0.9) |
| AE leading to d/c | 0 | 0 | 0 | 0 | 0 | 0 |
| Any SAE | 0 | 0 | 3 (0.8) | 0 | 1 (0.5) | 2 (1.9) |
| Number (%) of Subjects | <u>with</u> | <u>Abnormal</u> | <u>Skin</u> | <u>Assessment</u> | | |
| Erythema | 0 | 9 (8.2) | 46 (11.5) | 0 | 1 (0.5) | 8 (7.5) |
| Edema | 0 | 5 (4.5) | 19 (4.8) | 0 | 2 (1.0) | 4 (3.8) |
| Pruritus | ND | 3 (7.5) | 47 (13.4) | 1 (2.5) | 17 (9.4) | 22 (25.0) |
| Hemorrhage/Petechiae | 0 | 3 (2.7) | 48 (17.0) | 0 | 0 | 13 (43.3) |

Source: Amendment #007 (06/25/2007), Tables 10.1, 10.2 and 10.3, pages 16-18

Table 12-3 on page-128 presents early-device TEAEs, listing all PTs reported in ≥ 0.5% of subjects in any treatment group. Table 7-7 on page-35 summarizes these data by SOC only.

- Most AEs were localized to the treatment site, regardless of treatment condition
- Overall AE incidence, and treatment site related AE incidence were comparable between subjects treated with 0.50-mg/20-25-bar devices, and placebo/20-25-bar devices.
- In both active-drug and placebo-device treated subjects, "Application site disorders" occurred more frequently with higher device pressure (>25-bar)
 - It is not possible, however, to assess the relative roles of increases in device pressure, and increases in lidocaine dose; the >25-bar devices only administered lidocaine doses >0.50-mg
 - Several PTs within this SOC, though, were actually more frequent with 20-25 bar devices than with devices >25-bar (i.e., injection site bruising, injection site bleeding)
- Differences between treatment groups in PT incidence rates are likely attributable, at least in part, to small numbers of patients within each treatment group, and overall low AE frequency

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Table 7-7: TEAEs by WHO-ART System Organ Class, Early-Device Studies

| WHO-ART System Organ Class | 0.50-mg/ 20-25-bar | | >0.50-mg/ 20-25-bar | | >0.50-mg/ >25-bar | | Placebo/ 20-25-bar | | Placebo/ >25-bar | | Mannitol (Placebo) | |
|--|-----------------------|----|------------------------|----|----------------------|----|-----------------------|----|---------------------|---|-----------------------|----|
| | N=60 | % | N=110 | % | N=400 | % | N=140 | % | N=202 | % | N=106 | % |
| Application Site Disorders | 11 | 18 | 48 | 44 | 68 | 17 | 28 | 20 | 18 | 9 | 29 | 27 |
| Central/Peripheral Nervous System D/Os | 7 | 12 | 20 | 18 | 17 | 4 | 20 | 14 | 2 | 1 | 10 | 9 |
| Respiratory System Disorders | 6 | 10 | 14 | 13 | 18 | 5 | 14 | 10 | 6 | 3 | 10 | 9 |
| Skin and Appendages Disorders | 6 | 10 | 39 | 36 | 21 | 5 | 15 | 11 | 6 | 3 | 4 | 4 |
| Body As a Whole—General Disorders | 2 | 3 | 5 | 5 | 22 | 6 | 5 | 4 | 8 | 4 | 12 | 11 |
| Musculoskeletal System Disorders | 2 | 3 | 5 | 5 | 0 | 0 | 5 | 4 | 0 | 0 | 0 | 0 |
| Platelet, Bleeding, Clotting Disorders | 2 | 3 | 15 | 14 | 83 | 21 | 5 | 4 | 8 | 4 | 24 | 23 |
| Gastrointestinal System Disorders | 1 | 2 | 5 | 5 | 16 | 4 | 5 | 4 | 6 | 3 | 4 | 4 |
| Autonomic Nervous System Disorders | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 |
| Cardiovascular Disorders | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2 | 1 | 1 | 1 |
| Hearing and Vestibular Disorders | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 1 | 1 | 0 | 0 |
| Heart Rate and Rhythm Disorders | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| Liver and Biliary System Disorders | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| Metabolic and Nutritional Disorders | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| Other Adverse Events | 0 | 0 | 0 | 0 | 4 | 1 | 0 | 0 | 1 | 1 | 1 | 1 |
| Psychiatric Disorders | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 1 | 1 | 1 | 1 |
| Resistance Mechanism Disorders | 0 | 0 | 0 | 0 | 13 | 3 | 0 | 0 | 4 | 2 | 4 | 4 |
| Secondary Terms | 0 | 0 | 7 | 6 | 7 | 2 | 7 | 5 | 1 | 1 | 5 | 5 |
| Urinary System Disorders | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Vascular (Extra-cardiac) Disorders | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Vision Disorders | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |

Source: Modified from Amendment #006, Table-7, page-8

Late-Device Studies

Table 7-8 below summarizes AE incidence rates in the overall ND5.3A and ND5.3 studies (adult and pediatric), and from the controlled pediatric studies (3-003-1 and 3-004-1), by treatment group. In both populations similar proportions of LHM-treated and placebo-treated subjects treatment-emergent AEs (TEAEs), and treatment-related TEAEs.

Overall 7.9% of active-LHM-treated subjects experienced a TEAE, compared with 8.1% of placebo-treated subjects. In the controlled pediatric (final device) trials, 12.8% of active-LHM-treated subjects experienced a TEAE, compared with 13.2% of placebo-treated subjects.

The overall proportion of subjects with AEs was slightly lower in pediatric subjects than in adult subjects (9.2% vs. 10.4%). In both age groups, however, incidence and types of adverse events were similar between active-drug and placebo treated subjects.

The only differences in AE incidence, between active and placebo treated adults were:

- “Venipuncture site hemorrhage” (n=3 active (0.6%) and n=13 placebo (3.0%))
- “Dizziness” (n=6 active (1.2%) and n=1 placebo (0.2%))

By Anesiva’s assessment, in the nine late-device trials, 2.9% of active-LHM-treated subjects experienced a treatment-related AE, compared with 2.0% of placebo-treated subjects, while in the two controlled pediatric trials, 3.0% and 2.4% of active and placebo-treated subjects, respectively experienced treatment-related AEs. My review of the adverse event data, though hampered somewhat by lack of information (i.e., CRFs, narrative summaries), finds the Anesiva reported incidence rates likely to be reasonably accurate. That is, 60%-80% of all TEAE (in each treatment arm, for both the ND5.3+ND5.3A, and the ND5.3A only populations), appear unlikely to have been related to study treatment (i.e., musculoskeletal strains and sprains).

Table 7-8: Safety Overview - Adverse Events in Late-Device Trials (ND5.3 and ND5.3A Studies)

| Number (%) of Subjects | ND5.3A and ND5.3 | | Controlled Pediatric | |
|---------------------------|-------------------|-----------------------|----------------------|----------------------|
| | LHM N=1389 (%) | Placebo N=1282 (%) | LHM N=561 (%) | Placebo N=553 (%) |
| Any AE | 110 (7.9) | 104 (8.1) | 72 (12.8) | 73 (13.2) |
| Related AE, my assessment | (<3.5%) | (<2.5%) | (<3.5%) | (<2.5%) |
| Related AE, per Anesiva | 40 (2.9) | 25 (2.0) | 17 (3.0) | 13 (2.4) |
| “Severe AE” | 4 (0.3) | 3 (0.2) | 0 (0) | 0 (0) |
| AE leading to d/c | 2 (0.1) | 2 (0.2) | 0 (0) | 0 (0) |
| Any SAE | 5 (0.4) | 3 (0.2) | 1 (0.2) | 2 (0.4) |

Source: Data listings 14.3.2.1, 14.3.3.1, 14.3.4, 14.4.1, ISS Tables 7.2.1, 7.3.1, 7.4 and 7.5, AETESS1.XPT datasets

Minor, transient skin changes (at the treatment site) were far more common than adverse events, local or systemic. “Non-abnormal” post-treatment dermal changes are summarized in the form of shift-tables on page 46 through on page 49 below (Table 7-13 through Table 7-16).

“Abnormal skin site assessments” were defined prospectively as skin site assessments, at any time-point, within the top two grades for each of the four measured skin assessments (erythema, edema, pruritus, and hemorrhage/petechiae). Incidence rates (Table 7-9 below) were as follows:

- Erythema Grades 3 and 4 “moderate to severe erythema” and “severe erythema to slight eschar formation,” occurred in 2.1% vs. 0% of subjects receiving LHM and placebo, respectively.
- Hemorrhage/Petechiae Grades 4 and 5 was uncommon overall, but reported more frequently in active (0.9%) than in placebo treated (0%) subjects.
- “Abnormal” edema occurred with similar frequency in the active and placebo groups.
- “Abnormal” pruritus occurred with similar frequency in the active and placebo groups.

Table 7-9: Safety Overview – Abnormal* Post-Treatment Skin Assessment

| | ND5.3A and ND5.3 | | Controlled Pediatric | |
|-------------------------------|----------------------|------------------------|----------------------|----------------------|
| | LHM N=1389 (%) | Placebo N=1282 (%) | LHM N=561 (%) | Placebo N=553 (%) |
| Number (%) of Subjects | <u>with Abnormal</u> | <u>Skin Assessment</u> | | |
| Erythema | 29 (2.1) | 0 (0.0) | 4 (0.7) | 0 (0) |
| Edema | 2 (0.1) | 0 (0.0) | 0 (0) | 0 (0) |
| Pruritus | 26 (1.9) | 18 (1.4) | 1 (0.2) | 1 (0.2) |
| Hemorrhage/Petechiae | 12 (0.9) | 0 (0.0) | 9 (1.6) | 0 (0) |

Source: Data listings 14.3.2.1, 14.3.3.1, 14.3.4, 14.4.1 and ISS Tables 7.2.1, 7.3.1, 7.4 and 7.5 per Anesiva

Twelve subjects (9 pediatric, 3 adult) experienced “abnormal” hemorrhage or petechiae. All had been treated with active LHM; none were placebo-treated. Narrative summaries were provided for each of these subjects, indicating marked improvement in most by 24-hours (post-RX). Complete resolution by 48-hours was reported in seven of the twelve, and by 96-hours for the remaining five. Review of these subjects’ data line listings shows no AEs reported on telephone follow-up (48-hours and 7-days).

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Treatment site skin assessments were summarized by worst grade at any time-point (Table 7-10).

Table 7-10: Treatment Site Assessments, by Worst Grade Achieved, Number (%) of Subjects

| | ACTIVE | | PLACEBO | |
|---------------------------------|----------------------------------|----------------------|----------------------------|----------------------|
| | 0.5mg/20-21-bar N=1031 | ALL N=1389 | 20-21-bar N=1064 | ALL N=1281 |
| Erythema | | | | |
| 0) None | 407 (39.5) | 495 (35.6) | 744 (69.9) | 890 (69.5) |
| 1) Very slight | 373 (36.2) | 466 (33.5) | 287 (27.0) | 352 (27.5) |
| 2) Well-defined | 239 (23.2) | 399 (28.7) | 33 (3.1) | 39 (3.0) |
| 3) Moderate to severe | 12 (1.2) | 29 (2.1) | 0 (0.0) | 0 (0.0) |
| 4) Severe to eschar formation | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Edema | | | | |
| 0) None | 954 (92.5) | 1303 (93.8) | 1035 (97.3) | 1252 (97.7) |
| 1) Very slight | 70 (6.8) | 76 (5.5) | 27 (2.5) | 27 (2.1) |
| 2) Slight | 7 (0.7) | 8 (0.6) | 2 (0.2) | 2 (0.2) |
| 3) Moderate | 0 (0.0) | 2 (0.1) | 0 (0.0) | 0 (0.0) |
| 4) Severe | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Pruritis | | | | |
| 0) None | 988 (95.8) | 1301 (93.7) | 1032 (97.0) | 1229 (95.9) |
| 1) Occasional | 30 (2.9) | 62 (4.5) | 20 (1.9) | 34 (2.7) |
| 2) Constant | 13 (1.3) | 26 (1.9) | 12 (1.1) | 18 (1.4) |
| Hemorrhage/Petechiae | | | | |
| 0) None | 573 (55.6) | 745 (53.6) | 1004 (94.4) | 1207 (94.2) |
| 1) ≤ 5-isolated | 164 (15.9) | 230 (16.6) | 50 (4.7) | 63 (4.9) |
| 2) >5-isolated | 208 (20.2) | 290 (20.9) | 9 (0.8) | 10 (0.8) |
| 3) Many petechiae | 77 (7.5) | 112 (8.1) | 1 (0.1) | 1 (0.1) |
| 4) Numerous or surface bleeding | 8 (0.8) | 10 (0.7) | 0 (0.0) | 0 (0.0) |
| 5) Frank bleeding | 1 (0.1) | 2 (0.1) | 0 (0.0) | 0 (0.0) |

Source: ISS Appendix Table-4.2.1

Information about (skin change) time to resolution is limited to the data as presented above. Anesiva does, however, state that skin changes resolved prior to discharge in all but "... a few" subjects, and that all subjects reported complete resolution by the 48-72 hour follow-up phone call.

Anesiva also summarized, by treatment group:

- All occurrences of erythema, edema, pruritus, and hemorrhage/petechiae
- Patients with erythema and edema greater than Grade 2
- Patients with hemorrhage/petechiae of greater severity than Grade 3
- Patients with pruritus of greater severity than Grade 1

No differences were apparent between active-drug and placebo-device treated subjects.

7.1.5.4 Common adverse event tables

Table 7-11 and Table 7-12 below summarize treatment-emergent adverse events reported during the nine late-device trials. Few differences were found, between active-device and placebo-device subjects. Where differences do exist, clinical significance is expected to be negligible.

There were no studies using zero-pressure devices; all subjects were treated with pressurized helium (most at 20-21 bar). It is not possible to ascertain, from the studies conducted, whether adverse events and skin reactions may have been attributable to the delivery system/device, and not necessarily to the active drug. Nevertheless, adverse events and appreciable skin changes were limited both in frequency and severity, demonstrating a relatively benign safety profile.

Overall, 7.9% of active-LHM treated subjects and 8.1% of placebo-treated subjects experienced an adverse event. In both groups, most of these were application site reactions, categorized under SOC *General disorders and administrative site conditions* (2.4% and 3.4%, in active and placebo treated subjects, respectively), or under SOC *Skin & subcutaneous tissue disorders* (1.2% and 0.9%, in active and placebo treated subjects, respectively).

The incidence of application site reactions categorized under *General disorders and administrative site conditions* was slightly higher in 40-bar treated subjects than in those treated with 20-bar devices (both active-drug and placebo). The incidence of *Skin & subcutaneous tissue disorders*, though, was actually lower in subjects treated with 40-bar devices than it was in those treated with 20-bar devices.

Adverse events categorized under SOC *Nervous system disorders*, occurred in about 1.5% of subjects, in both treatment groups (PT 'Dizziness' being most frequent). *Gastrointestinal disorders* were also relatively common, occurring in about 2% of subjects in both groups.

Anesiva's proposed label does not include tabular presentation of safety data (i.e., adverse events, skin findings). Instead, Anesiva includes (after a brief summary of exposure) the following text:

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b(4)

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Table 7-11: Treatment-Emergent Adverse Events Occurring in ≥ 0.5% of Subjects in Any Treatment Group: Late-Device Studies

| System Organ Class Preferred Term | ACTIVE | | | LHM TOTAL N=1389 | PLACEBO | | Placebo TOTAL N=1282 | ALL TOTAL N=2260 |
|--------------------------------------|-----------------------------|------------------------------|-----------------------------|------------------------|------------------------------|-----------------------------|----------------------------|------------------------|
| | 0.25-mg/ 20-bar N=134 | 0.50-mg/ 20-bar N=1031 | 0.50-mg/ 40-bar N=224 | | Placebo/ 20-bar N=1065 | Placebo/ 40-bar N=217 | | |
| Subjects with any AE (N) | 6 (4.5) | 97 (9.4) | 7 (3.1) | 110 (7.9) | 92 (8.6) | 12 (5.5) | 104 (8.1) | 214 (9.5) |
| General D/O, Admin. site conditions | 3 (2.2) | 24 (2.3) | 6 (2.7) | 33 (2.4) | 35 (3.3) | 9 (4.1) | 44 (3.4) | 77 (3.4) |
| Application site bruising | 0 (0.0) | 5 (0.5) | 0 (0.0) | 5 (0.4) | 9 (0.9) | 0 (0.0) | 9 (0.7) | 14 (0.6) |
| Application site burning | 1 (0.8) | 2 (0.2) | 2 (0.9) | 5 (0.4) | 4 (0.4) | 0 (0.0) | 4 (0.3) | 9 (0.4) |
| Venipuncture site hemorrhage | 0 (0.0) | 1 (0.1) | 2 (0.9) | 3 (0.2) | 4 (0.4) | 9 (4.2) | 13 (1.0) | 16 (0.7) |
| Pain NOS | 1 (0.8) | 1 (0.1) | 1 (0.5) | 3 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (0.1) |
| Venipuncture site bruise | 0 (0.0) | 2 (0.2) | 0 (0.0) | 2 (0.1) | 6 (0.6) | 0 (0.0) | 6 (0.5) | 8 (0.4) |
| Application site anesthesia | 1 (0.8) | 1 (0.1) | 0 (0.0) | 2 (0.1) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 3 (0.1) |
| Application site paresthesia | 1 (0.8) | 1 (0.1) | 0 (0.0) | 2 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.1) |
| Gastrointestinal disorders | 0 (0.0) | 24 (2.3) | 0 (0.0) | 24 (1.7) | 24 (2.3) | 2 (0.9) | 26 (2.0) | 50 (2.2) |
| Nausea | 0 (0.0) | 17 (1.7) | 0 (0.0) | 17 (1.2) | 17 (1.6) | 1 (0.5) | 18 (1.4) | 35 (1.6) |
| Vomiting NOS | 0 (0.0) | 7 (0.7) | 0 (0.0) | 7 (0.5) | 7 (0.7) | 0 (0.0) | 7 (0.6) | 14 (0.6) |
| Nervous system D/O | 1 (0.7) | 18 (1.7) | 1 (0.4) | 20 (1.4) | 13 (1.2) | 2 (0.9) | 15 (1.2) | 35 (1.5) |
| Dizziness | 0 (0.0) | 8 (0.8) | 0 (0.0) | 8 (0.6) | 2 (0.2) | 1 (0.5) | 3 (0.2) | 11 (0.5) |
| Burning sensation NOS | 1 (0.8) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 2 (0.1) |
| Skin & subcutaneous tissue D/O | 0 (0.0) | 16 (1.6) | 0 (0.0) | 16 (1.2) | 10 (0.9) | 1 (0.5) | 11 (0.9) | 27 (1.2) |
| Contusion | 0 (0.0) | 6 (0.6) | 0 (0.0) | 6 (0.4) | 6 (0.6) | 0 (0.0) | 6 (0.5) | 12 (0.5) |
| Injury/poisoning/procedure complic. | 1 (0.7) | 6 (0.6) | 0 (0.0) | 7 (0.5) | 3 (0.3) | 0 (0.0) | 3 (0.2) | 10 (0.4) |
| Spinal fracture NOS | 1 (0.8) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| Surgical & medical procedures | 1 (0.7) | 1 (0.1) | 0 (0.0) | 2 (0.1) | 2 (0.2) | 0 (0.0) | 2 (0.2) | 4 (0.2) |
| Hospitalization | 1 (0.8) | 1 (0.1) | 0 (0.0) | 2 (0.1) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 3 (0.1) |

Source: Modified from ISS Table -13 using dataset AETESS1.xpt

Table 7-12: Treatment-Emergent Adverse Events by MedDRA System Organ Class: Late-Device Studies

| System Organ Class | ACTIVE | | | LHM TOTAL | PLACEBO | | ALL TOTAL | |
|-------------------------------------|-----------------------------|------------------------------|-----------------------------|--------------|------------------------------|-----------------------------|--------------|----------------------------|
| | 0.25-mg/ 20-bar N=134 | 0.50-mg/ 20-bar N=1031 | 0.50-mg/ 40-bar N=224 | | Placebo/ 20-bar N=1065 | Placebo/ 40-bar N=217 | | Placebo TOTAL N=1282 |
| Subjects with any AE (N) | 6 (4.5) | 97 (9.4) | 7 (3.1) | 110 (7.9) | 92 (8.6) | 12 (5.5) | 104 (8.1) | 214 (9.5) |
| General D/O, Adm. site conditions | 3 (2.2) | 24 (2.3) | 6 (2.7) | 33 (2.4) | 35 (3.3) | 9 (4.1) | 44 (3.4) | 77 (3.4) |
| Gastrointestinal disorders | 0 (0.0) | 24 (2.3) | 0 (0.0) | 24 (1.7) | 24 (2.3) | 2 (0.9) | 26 (2.0) | 50 (2.2) |
| Nervous system D/O | 1 (0.7) | 18 (1.7) | 1 (0.4) | 20 (1.4) | 13 (1.2) | 2 (0.9) | 15 (1.2) | 35 (1.5) |
| Skin & subcutaneous tissue D/O | 0 (0.0) | 16 (1.6) | 0 (0.0) | 16 (1.2) | 10 (0.9) | 1 (0.5) | 11 (0.9) | 27 (1.2) |
| Injury/poisoning/procedure complic. | 1 (0.7) | 6 (0.6) | 0 (0.0) | 7 (0.5) | 3 (0.3) | 0 (0.0) | 3 (0.2) | 10 (0.4) |
| Vascular D/O | 0 (0.0) | 6 (0.6) | 0 (0.0) | 6 (0.4) | 4 (0.4) | 1 (0.5) | 5 (0.4) | 11 (0.5) |
| Cardiac D/O | 0 (0.0) | 6 (0.6) | 0 (0.0) | 6 (0.4) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 7 (0.3) |
| Respiratory, thoracic, mediast. D/O | 0 (0.0) | 5 (0.5) | 0 (0.0) | 5 (0.4) | 9 (0.8) | 0 (0.0) | 9 (0.7) | 14 (0.6) |
| Musculoskeletal/conn. tissue D/O | 0 (0.0) | 4 (0.4) | 0 (0.0) | 4 (0.3) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 5 (0.2) |
| Investigations | 0 (0.0) | 3 (0.3) | 0 (0.0) | 3 (0.2) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 4 (0.2) |
| Surgical & medical procedures | 1 (0.7) | 1 (0.1) | 0 (0.0) | 2 (0.1) | 2 (0.2) | 0 (0.0) | 2 (0.2) | 4 (0.2) |
| Metabolism and nutrition D/O | 0 (0.0) | 2 (0.2) | 0 (0.0) | 2 (0.1) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 3 (0.1) |
| Renal and urinary D/O | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 2 (0.2) | 0 (0.0) | 2 (0.2) | 3 (0.1) |
| Infections and infestations | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 2 (0.1) |
| Eye disorders | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| Immune system D/O | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| Psychiatric disorders | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.2) | 0 (0.0) | 2 (0.2) | 2 (0.1) |
| Ear and labyrinth D/O | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 1 (0.0) |
| Blood & lymphatic system D/O | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 1 (0.0) |

Source: Modified from ISS Table -12 using dataset AETESS11.xpt

7.1.5.5 Identifying common and drug-related adverse events

All adverse events were identified, whether reasonably considered drug related, or not. No consistent differences were identified, between active-drug and placebo-treated subjects. Also, although limited dose-ranging data were available, no clear dose-response was evident, for lidocaine-dose, or for device pressure.

7.1.5.6 Additional analyses and explorations

As noted in Section 7.1.5.5 above, there was no evidence that lidocaine dose, or device pressure affected AE incidence rates. Lidocaine dose, and device pressure increases were not associated with increases in AE incidence or severity.

Higher device pressure (40-bar) was, however, associated with a modest increase in the incidence of “very slight” to “moderate” edema, immediately post-treatment. Erythema in these cases resolved, however, as rapidly as for subjects treated with the 20-21 bar devices.

7.1.6 Less Common Adverse Events

Treatment-emergent adverse events, attributable to study treatment or otherwise, were infrequent, making identification of patterns of less frequent AEs infeasible. Nevertheless, noteworthy, rare AEs are described and discussed in Sections 7.1.2 above (Other SAEs) and 7.1.3.3 (Other Significant AEs).

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory testing during Zingo™ development was limited almost exclusively to screening assessment during Phase-1 (early device) studies only, except for pregnancy testing.

Phase-1 (Early Device) Studies

Table 7-13 below includes a summary of laboratory testing in the early-device studies.

- Screening laboratory testing (CBC, chemistry profile) was done in most early device trials, but follow-up laboratory testing was not performed
- Vital sign measures were obtained in seven studies (only at screening)
- ECGs were obtained in two studies (only at screening)
- Five of the fourteen studies called for dosing on more than one day
 - DPJ 01-001, D4115-023-CL and DPJ 01-005 called for two dosing sessions \geq one week apart.
- Multiple pregnancy tests were performed in these studies, as shown in Table 7-13 below.
 - D4115-001-CL and MDS-20643 enrolled only males
- D4115-023-CL and ICR-012770 incorporated hepatitis virus serology
- Screening for Study D4115-023-CL included urine toxicology
- Screening laboratory testing (CBC, chemistry profile) was performed in both pediatric, early-device studies (ICR-031086 and ICR-031091)

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Table 7-13: Safety Assessment in Early Device Trials

| Study | Device | Doses (Active) | Dosing Sessions | Screen Labs | F/U Labs | Virology | ECG ^b | Vitals ^b | Preg. | Utox |
|---------------------------|--------|----------------|-----------------|-------------|----------|----------|------------------|---------------------|-------|------|
| Adult | | | | | | | | | | |
| C96-101-01 | ND1 | 1 | 1 | X | -- | -- | -- | X | X | -- |
| DPJ 01-001 | ND1 | 4 | 2 | X | -- | -- | -- | X | X2 | -- |
| DPJ 01-002 | ND1 | 1 | 1 | -- | -- | -- | -- | X | X4 | -- |
| MDS-20643 ^a | ND1 | 2 | 2 | X | -- | -- | -- | X | NA | -- |
| ICR-012770 ^a | ND1 | 3 | 1 | X | -- | X | X | X | NA | -- |
| DPJ 01-003 ^a | ND1 | 3 | 1 | X | -- | -- | -- | -- | NA | -- |
| D4115-001-CL ^a | ND1 | 3 | 3 | X | -- | -- | -- | X | NA | -- |
| ICR-013727 | ND5 | 1 | 1 | -- | -- | -- | -- | -- | X | -- |
| D4115-023-CL | ND5.1 | 2 | 2 | X | -- | X | X | X | X4 | X |
| DPJ LID 009 | ND5.2 | 1 | 1 | -- | -- | -- | -- | -- | X | -- |
| DPJ 01-004 | ND5.2 | 1 | 1 | -- | -- | -- | -- | -- | X | -- |
| DPJ 01-005 | ND5.2 | 2 | 2 | X | -- | -- | -- | -- | X4 | -- |
| Pediatric | | | | | | | | | | |
| ICR-031086 | ND1 | 1 | 1 | X | -- | -- | -- | -- | -- | -- |
| ICR-031091 | ND1 | 1 | 1 | X | -- | -- | -- | -- | -- | -- |

^a Males only

^b Screening only

Source: Clinical reviewer

Phase-2/3 (Late Device) Studies

Table 7-14 below includes a summary of laboratory testing in the early-device studies.

Seven of the nine late device studies called only for a single treatment day. Two trials called for two sessions per subject, approximately one-week apart. (Dose finding Studies 1-100-001 and 1-102-001).

Of these nine trials, only two collected laboratory data (besides screening pregnancy testing):

- Open-label PK Study 1-101-001 collected post-treatment serial plasma lidocaine levels, but no screening laboratory data (PK assessment, N=38).
- Open-label Study 1-005-1 collected screening and post-treatment laboratory data (Sound emission assessment, N=6).

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Table 7-14: Safety Assessment in Late Device Trials

| | Design/ Device | Populat. | Doses (Active) | Dosing Sessions | Screen Labs | F/U Labs | ECG ^c | Vitals ^c | Preg. |
|-------------------------------|-------------------|----------|-------------------|--------------------|----------------|-------------|------------------|---------------------|----------------|
| Late Device | DB-XO | | | | | | | | |
| 1-100-001 ^a (Dose) | ND5.3 | Adult | 2 | 2 | -- | -- | -- | X | X3 |
| 1-102-001 ^a (Dose) | ND5.3 | Adult | 2 | 2 | -- | -- | -- | X | X3 |
| Late Device | OL | | | | | | | | |
| 1-101-001 (PK) | ND5.3 | Adult | 1 | 1 | X | Lidocaine | X | X | X1 |
| 1-005-1 (Sound) | ND5.3 | Adult | 4 | 1 | X | X | X | X | X1 |
| Late Device | DB-PG | | | | | | | | |
| 4-401-001 | ND5.3 | Peds | 1 | 1 | -- | -- | -- | -- | X ^b |
| 4-400-001 | ND5.3 | Peds | 1 | 1 | -- | -- | -- | -- | X ^b |
| 2-002-001 | ND5.3 | Peds | 1 | 1 | -- | -- | -- | -- | X ^b |
| Final Device | DB-PG | | | | | | | | |
| 3-003-1 | ND5.3A | Peds | 1 | 1 | -- | -- | -- | -- | X ^b |
| 3-004-1 | ND5.3A | Peds | 1 | 1 | -- | -- | -- | -- | X ^b |

^a Two dosing sessions ^b Per investigators' IRBs, adolescent only ^c Screening only

Source: Clinical reviewer

Pregnancy Testing

Overall, 18-trials enrolled both female and male subjects (all nine late-device trials, and 9/14 early-device trials). A negative screening pregnancy test (urine more often than blood) was required for participation, in all but one trial in which female adults were enrolled (multiple-session ICR-012770).

Nine studies called for dosing on more than one day; three of these enrolled only males. Follow-up pregnancy testing was conducted in five of the six remaining multiple session trials.

- Studies 1-100-001 and 1-102-001 called for two dosing sessions, separated by at least six-days. Pregnancy testing was done three times in these studies; at screening, and on both treatment days.
- Study D4115-023-CL called for two treatment sessions; the first within fourteen days of screening, and the second seven days later. Pregnancy testing was done at screening, and on both dosing days.
- Study DPJ-01-003 called for three treatment sessions. The first two were two-weeks apart. The third session took place 21 to 30 days after the second. Pregnancy testing was done four times; at screening, and prior to dosing on each treatment day.
- Study DPJ-01-005 called for two treatment sessions, five-weeks apart. Pregnancy testing was done a total of six times, three times for each of the two treatment sessions; at screening (and re-screening), pre-dose, and at the Day-15 follow-up visit.
- Entry criteria for three-session, ascending pressure Study ICR-012770 excluded "Females who are pregnant or lactating," but the protocol did not require pregnancy testing. The protocol appears not to have specified the inter-session interval, but review of the data listings shows that each subject's sessions were two-weeks apart.

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7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values
Not possible given the data collected.

7.1.7.3 Standard analyses and explorations of laboratory data
Not possible given the data collected.

7.1.7.3.1 Analyses focused on measures of central tendency

Not possible given the data collected.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Not possible given the paucity of laboratory data collected during product development.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Not possible given the paucity of laboratory data collected during product development.

7.1.7.4 Additional analyses and explorations

Post-treatment skin-changes rarely qualified as adverse events, but were carefully scrutinized. These findings are discussed along with adverse events, in Section 7.1.5 above.

7.1.7.4.1 Analyses focused on measures of central tendency

Not possible given the data collected.

7.1.7.4.2 Analyses focused on outliers or shifts from normal to abnormal

Not possible given the data collected.

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Table 7-15: Baseline to Post-Treatment Erythema, ND5.3A Pediatric Studies (3-003-1, 3-004-1)

| Time Point | Erythema Assessment | <u>ACTIVE</u> | <u>0.5-mg/21-bar</u> | <u>PLACEBO</u> | <u>0.0-mg/21-bar</u> |
|--|---------------------|----------------------------------|-----------------------------|----------------------------------|-----------------------------|
| | | <u>BASELINE</u> None Reported | <u>N=561</u> Very Slight | <u>BASELINE</u> None Reported | <u>N=553</u> Very Slight |
| < 1-Min. After RX | None | 401 (71.5) | 0 (0.0) | 465 (84.1) | 0 (0.0) |
| | Very slight | 135 (24.1) | 1 (0.2) | 83 (15.0) | 2 (0.0) |
| | Well defined | 23 (4.1) | 0 (0.0) | 3 (0.5) | 0 (0.0) |
| | Moderate to severe | 1 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Severe to eschar | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Not reported | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 15-Mins. After RX | None | 241 (43.0) | 0 (0.0) | 385 (69.6) | 0 (0.0) |
| | Very slight | 238 (42.4) | 1 (0.2) | 147 (26.6) | 2 (0.4) |
| | Well defined | 76 (13.5) | 0 (0.0) | 16 (2.9) | 0 (0.0) |
| | Moderate to severe | 3 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Severe to eschar | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Not reported | 2 (0.4) | 0 (0.0) | 3 (0.5) | 0 (0.0) |
| 30-Mins. After RX | None | 266 (47.4) | 0 (0.0) | 426 (77.0) | 0 (0.0) |
| | Very slight | 223 (39.8) | 1 (0.2) | 113 (20.4) | 2 (0.4) |
| | Well defined | 66 (11.8) | 0 (0.0) | 7 (1.3) | 0 (0.0) |
| | Moderate to severe | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Severe to eschar | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Not reported | 5 (0.9) | 0 (0.0) | 5 (0.9) | 0 (0.0) |
| 1-3 Hours After RX Only if Earlier ≥ Grade-3 | None | 0 (0.0) | 0 (0.0) | 2 (0.4) | 0 (0.0) |
| | Very slight | 1 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Well defined | 1 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Moderate to severe | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Severe to eschar | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Not reported | 558 (99.5) | 1 (0.2) | 549 (99.3) | 2 (0.4) |

Source: ISS Appendix Table-4.2.1

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Table 7-16: Baseline to Post-Treatment Edema, ND5.3A Pediatric Studies (3-003-1, 3-004-1)

| Time Point | Edema Assessment | <u>ACTIVE</u> | <u>0.5-mg/21-bar</u> | <u>PLACEBO</u> | <u>0.0-mg/21-bar</u> |
|--|-------------------|-----------------|----------------------|-----------------|----------------------|
| | | <u>BASELINE</u> | <u>N=561</u> | <u>BASELINE</u> | <u>N=553</u> |
| | | None Reported | Very Slight | None Reported | Very Slight |
| < 1-Min. After RX | No edema | 554 (98.8) | 0 (0.0) | 550 (99.5) | 0 (0.0) |
| | Very slight edema | 4 (0.7) | 0 (0.0) | 3 (0.5) | 0 (0.0) |
| | Slight edema | 3 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Moderate edema | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Severe edema | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Not reported | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 15-Mins. After RX | No edema | 513 (91.4) | 0 (0.0) | 533 (96.4) | 0 (0.0) |
| | Very slight edema | 42 (7.5) | 0 (0.0) | 16 (2.9) | 0 (0.0) |
| | Slight edema | 4 (0.7) | 0 (0.0) | 1 (0.2) | 0 (0.0) |
| | Moderate edema | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Severe edema | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Not reported | 2 (0.4) | 0 (0.0) | 3 (0.5) | 0 (0.0) |
| 30-Mins. After RX | No edema | 512 (91.3) | 0 (0.0) | 532 (96.2) | 0 (0.0) |
| | Very slight edema | 42 (7.5) | 0 (0.0) | 15 (2.7) | 0 (0.0) |
| | Slight edema | 2 (0.4) | 0 (0.0) | 1 (0.2) | 0 (0.0) |
| | Moderate edema | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Severe edema | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Not reported | 5 (0.9) | 0 (0.0) | 5 (0.9) | 0 (0.0) |
| 1-3 Hours After RX Only if Earlier ≥ Grade-3 | No edema | 2 (0.4) | 0 (0.0) | 2 (0.4) | 0 (0.0) |
| | Very slight edema | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Slight edema | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Moderate edema | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Severe edema | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Not reported | 559 (99.6) | 0 (0.0) | 551 (99.6) | 0 (0.0) |

Source: ISS Appendix Tables 4.2.2

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Table 7-17: Baseline to Post-Treatment Pruritis, ND5.3A Pediatric Studies (3-003-1, 3-004-1)

| Time Point | Pruritis Assessment | <u>ACTIVE</u> 0.5-mg/21-bar | | <u>PLACEBO</u> 0.0-mg/21-bar | |
|---|---------------------|-----------------------------|------------|------------------------------|------------|
| | | <u>BASELINE</u> | | <u>BASELINE</u> | |
| | | No Pruritis | Occasional | No Pruritis | Occasional |
| < 1-Min. After RX | No pruritus | 561 (100.0) | 0 (0.0) | 552 (99.8) | 0 (0.0) |
| | Occasional | 0 (0.0) | 0 (0.0) | 1 (0.2) | 0 (0.0) |
| | Constant | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Not reported | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 15-Mins. After RX | No pruritus | 543 (96.8) | 0 (0.0) | 537 (97.1) | 0 (0.0) |
| | Occasional | 2 (0.4) | 0 (0.0) | 2 (0.4) | 0 (0.0) |
| | Constant | 1 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Not reported | 15 (2.7) | 0 (0.0) | 14 (2.5) | 0 (0.0) |
| 30-Mins. After RX | No pruritus | 532 (94.8) | 0 (0.0) | 525 (94.9) | 0 (0.0) |
| | Occasional | 4 (0.7) | 0 (0.0) | 3 (0.5) | 0 (0.0) |
| | Constant | 0 (0.0) | 0 (0.0) | 1 (0.2) | 0 (0.0) |
| | Not reported | 25 (4.5) | 0 (0.0) | 24 (4.3) | 0 (0.0) |
| 1-3 Hours After RX Only if Earlier (+) | No pruritus | 2 (0.4) | 0 (0.0) | 2 (0.4) | 0 (0.0) |
| | Occasional | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Constant | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Not reported | 559 (99.6) | 0 (0.0) | 551 (99.6) | 0 (0.0) |

Source: ISS Appendix Table-4.2.3

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Table 7-18: Baseline to Post-RX Hemorrhage/Petechiae, ND5.3A Pediatric Studies (3-003-1, 3-004-1)

| Time Point | Petechiae Assessment | <u>ACTIVE</u> | <u>0.5-mg/ 21-bar</u> | <u>0.5-mg/ 21-bar</u> | <u>PLACEBO</u> | <u>0.0-mg/ 21-bar</u> |
|------------|----------------------|-----------------|---------------------------|---------------------------|-----------------|---------------------------|
| | | <u>BASELINE</u> | <u>N=561</u> | <u>N=561</u> | <u>BASELINE</u> | <u>N=553</u> |
| | | None | ≤ 5 Isolated | > 5 Isolated | None | ≤ 5 Isolated |
| < 1-Min. | None | 321 (57.2) | 0 (0.0) | 0 (0.0) | 533 (96.4) | 0 (0.0) |
| After RX | ≤ 5 isolated | 94 (16.8) | 1 (0.2) | 0 (0.0) | 15 (2.7) | 0 (0.0) |
| | > 5 isolated | 127 (22.6) | 0 (0.0) | 0 (0.0) | 5 (0.9) | 0 (0.0) |
| | Many petechiae | 8 (1.4) | 0 (0.0) | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| | Numerous petechiae | 8 (1.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Frank bleeding | 1 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Not reported | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | 15-Mins. | None | 275 (49.0) | 0 (0.0) | 0 (0.0) | 517 (93.5) |
| After RX | ≤ 5 isolated | 100 (17.8) | 1 (0.2) | 0 (0.0) | 30 (5.4) | 0 (0.0) |
| | > 5 isolated | 129 (23.0) | 0 (0.0) | 0 (0.0) | 3 (0.5) | 0 (0.0) |
| | Many petechiae | 51 (9.1) | 0 (0.0) | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| | Numerous petechiae | 2 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Frank bleeding | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Not reported | 2 (0.4) | 0 (0.0) | 0 (0.0) | 3 (0.5) | 0 (0.0) |
| 30-Mins. | None | 279 (49.7) | 0 (0.0) | 0 (0.0) | 524 (94.8) | 0 (0.0) |
| After RX | ≤ 5 isolated | 113 (20.1) | 0 (0.0) | 0 (0.0) | 21 (3.8) | 0 (0.0) |
| | > 5 isolated | 110 (19.6) | 1 (0.2) | 0 (0.0) | 3 (0.5) | 0 (0.0) |
| | Many petechiae | 52 (9.3) | 0 (0.0) | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| | Numerous petechiae | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Frank bleeding | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Not reported | 5 (0.9) | 0 (0.0) | 0 (0.0) | 5 (0.9) | 0 (0.0) |
| 1-3 Hours | None | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.4) | 0 (0.0) |
| After RX | ≤ 5 isolated | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | > 5 isolated | 1 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Earlier | Many petechiae | 1 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Numerous petechiae | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| ≥ Grade-3 | Frank bleeding | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Not reported | 557 (99.3) | 1 (0.2) | 1 (0.2) | 551 (99.6) | 0 (0.0) |

Source: ISS Appendix Table-4.2.4

7.1.7.4.3 *Marked outliers and dropouts for skin abnormalities*

Only one study dropout seems reasonably attributable to a skin abnormality. Subject 1-100-001-204, a 19-year-old male with no significant PMH (and no concomitant medications), had no changes on skin assessments during the two-hours following treatment, except for Grade-1 treatment-site pruritus at 30-minutes (right ACF). He reported generalized urticaria two-days following placebo treatment, for which he was discontinued by the investigator, and treated with oral diphenhydramine (resolution < 2-days). Generalized urticaria reaction could, conceivably have been a type of dermatographia, resulting from dermal exposure to pressure alone. This seems exceedingly unlikely, however, given the subject's lack of allergic or atopic history.

7.1.7.5 Special assessments

[See Section 7.1.5.1 above for description of skin assessment methodology]

[See Section 7.1.12 below for discussion of Study 1-005-1, assessment of device sound emission]

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

During product development, vital signs were measured almost exclusively during study screening periods. Vital sign measurement during the early-device studies is summarized in Table 7-13 above.

Phase-2/3

Except for the sound emission study (1-005-1), vital signs were recorded only at screening, not after study treatment. In 1-005-1 no clinically relevant changes from screening were apparent. "Mean changes from baseline blood pressure and heart rate measurements on the day of Study Drug administration (at 15 and 30 minutes following Study Drug administration) and at the follow-up visit were small and not clinically relevant."

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons
Not applicable.

7.1.8.3 Standard analyses and explorations of vital signs data
Not possible, given the paucity of vital sign data.

7.1.8.3.1 *Analyses focused on measures of central tendencies*
Not applicable

7.1.8.3.2 *Analyses focused on outliers or shifts from normal to abnormal*
Not applicable

7.1.8.3.3 *Marked outliers and dropouts for vital sign abnormalities*
Not applicable

7.1.8.4 Additional analyses and explorations
Not applicable.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program

ECG acquisition was limited to one early-device study, and late-device Study 1-005-1. Only screening tests were obtained. ECG abnormalities at baseline precluded study participation.

Phase-1

ECGs were obtained in two early-device studies, ICR-012770 and D4115-023-CL, only at screening.

Phase-2/3

Except for the sound emission study (1-005-1), ECGs were not recorded after study treatment. In this study, no clinically relevant changes from screening were apparent. No subject had a clinically significant change from baseline ECG finding, although one subject (001-001) had sinus bradycardia at the screening visit (not clinically significant) that was not observed on the follow-up visit ECG.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable.

7.1.9.3.1 Analyses focused on measures of central tendency

Not applicable.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Not applicable.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Not applicable.

7.1.9.4 Additional analyses and explorations

Not applicable.

7.1.10 Immunogenicity

Immunogenicity assessment was not conducted.

7.1.11 Human Carcinogenicity

No specific human carcinogenicity studies were conducted during product development. My review of the safety data (ISS and individual study datasets, and study reports) identified no malignancies reported (during clinical trials or their pre-specified follow-up periods).

7.1.12 Special Safety Study (1-005-1).

Open-label Study 1-005-1 was conducted in six healthy adult volunteers (September 2005), in order to measure sound emission levels produced with use of the LHM device. Healthy adults without dermal conditions or pathologies were eligible to enroll. Potential subjects who had undergone BOH or ACF venipuncture or IV cannulation within the preceding two-weeks were excluded.

On the single treatment day (\leq two-weeks of screening), the N5.3A device was administered at four sites (on the back of each hand and on each antecubital fossa), in a predetermined random sequence. Administrations were separated by 15-minutes. Subjects returned 1-3 days post-RX for follow-up.

The primary measure was the sound level (in decibels) emitted by actuation of the LHM device. All sound measurements were obtained in one of two (identical) dedicated rooms (volume 30 m³). Subjects were placed in the standing position, with the application site supported by a stand 116-cm above the floor. Sound levels were measured in compliance with the ISO/FDIS 21649 standard. Three microphones were positioned, each 50-cm from the LHM device, using custom stands, a laser leveler, and a steel ruler. The C-weighted peak, and the A-weighted single event emission sound pressure levels, L_{pC} peak and L_{pA} 1s, respectively, were measured and recorded.

C-weighted peak sound levels exceeded 125-dB in one of 24 device actuations (130-dB proposed for marketed device). During one of two back-of-hand measures for Subject 1-005-1-006, the investigator noted immediately after device actuation, what he thought to be an inadequate seal; the z-axis recorded a maximum sound level of 135.6 dB(C). Sound levels are summarized in Table 7-19 below.

There were no appreciable differences in mean L_{pC} peak sound pressure levels between skin sites, 119.5 dB(C) recorded for the back of the hand and 118.1 dB(C) for the antecubital fossa. Sound pressure levels were reduced in L_{pA}-1s relative to L_{pC} peak levels, but there was no appreciable difference in log mean L_{pA} 1s sound levels between skin sites, 87.4 dB(A) was recorded for the back of the hand and 84.8 dB(A) for the antecubital fossa.

Table 7-19: Sound Levels Emitted from LHM Device (ITT)

| | Back of Hand | Antecubital Fossa |
|----------------------------------|----------------|-------------------|
| L_{pC}peak, dB(C) | | |
| n | 36 | 36 |
| Mean (SD) | 119.5 (4.1) | 118.1 (3.4) |
| Median | 119.2 | 117.7 |
| Range | 111.3 to 135.6 | 111.7 to 125.0 |
| L_{pA} 1s, dB(A) | | |
| n | 36 | 36 |
| Log Mean | 87.4 | 84.8 |
| Mean (SD) | 84.6 (3.5) | 84.1 (2.5) |
| Median | 83.8 | 83.7 |
| Range | 80.5 to 99.3 | 80.6 to 89.0 |

L_{pA} 1s A-weighted single-event emission sound pressure levels

L_{pC} peak C-weighted peak emission sound Source: 1-005-1 report Table 11-2

Skin site reactions were graded as for the other late-device studies. Additional safety assessments consisted of vital signs measurements, physical examination findings, clinical laboratory test results, pregnancy testing, electrocardiographic findings, skin site assessments, concomitant medication use, and collection of adverse events.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No specific studies were conducted, intended to assess the potential for product abuse or withdrawal. Review of the adverse event data listings and CRFs identified no cases suggestive of, or consistent with, abuse or withdrawal.

7.1.14 Human Reproduction and Pregnancy Data

There were no reported cases in which pregnant women were inadvertently enrolled and treated, nor were any new pregnancies identified (between sessions in crossover studies, or during follow-up).

7.1.15 Assessment of Effect on Growth

No specific studies were conducted, intended to assess product potential for affecting human growth. Although most human exposure occurred in pediatric-aged subjects, follow-up periods were brief hours to days), and serial height, weight or bone density measurements not obtained.

7.1.16 Overdose Experience

No cases of overdose were reported, either intentional or accidental. My review of the safety data (AE datasets and line listings, CRFs and individual study reports) identified no cases suggestive of, or consistent with overdose.

7.1.17 Postmarketing Experience

The Zingo™ product has not been approved anywhere in the world, as of July 10, 2007.

7.2 Adequacy of Patient Exposure and Safety Assessment

Overall, product exposure was sufficient for adequate safety review of single-dose exposure in the pediatric population (healthy, acutely ill and chronically ill). The adult exposure data alone would not be sufficient to allow for safety review in the adult population. Dermal findings from pediatric exposure can likely be extrapolated to the healthy, (non-elderly) adult population, however; pediatric skin is generally more vulnerable to topical drug induced acute injury than healthy adult skin. This extrapolation cannot be made for the elderly population, however, and only seven subjects over 65 years of age are included in the late-device safety database.

A total of 1919 subjects and patients (of 2870-enrolled) received treatment with the LHM product, in 23 completed clinical studies. Details are provided in Sections 7.2.1.1 and 7.2.1.2 below.

7.2.1 Primary Clinical Data Sources Used to Evaluate Safety (Populations, Exposure)

Two safety populations are described in the ISS. The first population consists of all nine ND5.3A and ND5.3 study subjects. It includes all adult and pediatric subjects treated with, what the applicant describes as “non-prototype devices.” The applicant refers to this as the “ND5.3A and ND5.3 Studies” population. These nine studies included the use of several configurations of dose and pressure, thus some safety data is presented by dose and pressure.

The second population consists only of subjects from the two controlled pediatric studies utilizing the final to-be-marketed device (ND5.3A); Studies 3-003-1 and 3-004-1. The applicant refers to this as the “ND5.3A Controlled Pediatric Studies” population.

7.2.1.1 Study type and design/patient enumeration

Phase-1 (Early Device Studies)

Fourteen studies were conducted with early prototypes of the _____ twelve in adults and two in pediatric subjects. **b(4)**

The two pediatric studies (ICR-031091 and ICR-031086) used a parallel group design. Each subject received a single treatment, either lidocaine 3.0-mg or placebo, to the antecubital fossa (ACF) or (back of hand) BOH. Delivery pressures studied were 30-bar and 40-bar.

The adult studies all utilized within-subject, crossover designs. Each subject served as their own control, usually receiving one placebo dose for each active-drug dose administered (to the opposite limb, or side of the body), roughly five-minutes apart.

The highest lidocaine dose administered, 5.0-mg, was administered in only one study, DJP-01-001 (2-mg, 3-mg and 5-mg, at 20-bar and 40-bar.) Otherwise, the early device studies evaluated 0.25-mg to 3.0-mg lidocaine doses (at 20-bar to 60-bar), with most including the 3.0-mg dose. Both pediatric early device studies administered 3.0-mg lidocaine doses at 30-bar and at 40-bar. The last four early-device studies evaluated lidocaine doses ranging from 0.50-mg to 3.0-mg (at 20 to 30-bar).

**Table 7-20: Adult Early-Device Studies
Doses and Pressures Evaluated, Number of Treatments and Study Sessions per Subject**

| Study | Device | N | Doses (mg) | Pressures (bar) | Treatments ^a /Subject | Treatment Sessions |
|-------------------------|--------|----|------------|-----------------|----------------------------------|--------------------|
| Adult | | | | | | |
| C96-101-01 | ND1 | 14 | 3 | 30 | 1 | 1 |
| DPJ 01-001 ^a | ND1 | 18 | 2, 3, 5 | 40, 60 | 4 | 2 |
| DPJ 01-002 ^a | ND1 | 40 | 3 | 40 | 1 | 1 |
| MDS-20643 | ND1 | 20 | 3 | 40 | 2 | 2 |
| ICR-012770 ^a | ND1 | 18 | 3 | 40, 60, 80 | 3 | 1 |
| DPJ 01-003 | ND1 | 30 | 3 | 40, 50, 60 | 3 | 1 |
| D4115-001-CL | ND1 | 8 | 3 | 40 | 3 | 3 |
| ICR-013727 | ND5 | 41 | 3 | 30 | 1 | 1 |
| D4115-023-CL | ND5.1 | 40 | 3 | 30 | 2 | 2 |
| DPJ LID 009 | ND5.2 | 20 | 0.5, 1, 2 | 20, 25, 30 | 1 | 1 |
| DPJ 01-004 | ND5.2 | 40 | 3 | 20 | 1 | 1 |
| DPJ 01-005 | ND5.2 | 80 | 0.5, 1 | 20, 25 | 2 | 2 |

^a One or more active-drug doses, with at least one placebo dose

Source: Clinical reviewer

The anatomic sites studied were the antecubital fossa (ACF), back of hand (BOH), lateral forearm, volar forearm, deltoid, lateral knee, midline back, and mid-axillary chest wall. Subjects were treated at:

- One or two (pairs of) anatomic sites, in eight studies
 - Five single-session studies, and three two-session studies (one to five weeks apart)
- Three (pairs of) anatomic sites, in three studies
 - Two single-session studies, and one three-session study (one week apart)
- Four (pairs of) anatomic sites, in one study, in two-treatment sessions

Phase-2/3 (ND5.3 and ND5.3 A Studies, or 'Late-Device' Studies)

Seven of the nine late device studies were double-blind, placebo-controlled trials, while two were open-label safety studies. Only two of these seven trials called for two treatment sessions per subjects (Dose finding Studies 1-100-001 and 1-102-001 in adults). The remaining five (4-401-001, 4-400-001, 2-002-001, 3-003-001, and 3-004-001) were pediatric only, parallel-group, single-dose trials.

All five pediatric studies utilized a parallel group design, in which subjects received either active drug or placebo; 906 received LHM while 855 received placebo. The two adult trials (1-100-1 and 1-102-1)

utilized a crossover design, in which each subject received LHM once or twice, and placebo once. These two studies enrolled a total of 499-adults (including replacement subjects), most of whom received single doses of both LHM and of placebo.

Only Studies 3-003-1 and 3-004-1 utilized the final, to-be-marketed device (ND5.3A).

Table 7-21 below summarizes relevant details from the nine late-device studies.

Table 7-21: Studies Utilizing the ND5.3 and ND5.3A (Final) Devices, Reviewed for Safety Findings

| Study | 1-101-1 | 1-100-1 | 1-102-1 | 4-401-1 | 4-400-1 | 2-002-1 | 3-003-1 | 3-004-1 | 1-005-1 |
|-------------------|-------------------|--------------------|-------------------|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Population | Adult | Adult | Adult | Pediatric | Pediatric | Pediatric | Pediatric | Pediatric | Adult |
| Objective | PK | Dose-ranging | Dose-ranging | Dose-ranging | Dose-ranging | Phase-3 | Phase-3 | Phase-3 | Sound assess. |
| Device Used | ND5.3 | ND5.3 | ND5.3 | ND5.3 | ND5.3 | ND5.3 | ND5.3A | ND5.3A | ND5.3A |
| Pain Model | None | VP | VP | VP | VP | VP | VP/IV | VP/IV | None |
| Body Site | ACF | ACF | BOH | ACF | BOH | BOH | BOH/ACF | BOH/ACF | BOH/ACF |
| Number | 38 | 272 | 183 | 145 | 195 | 307 | 579 | 585 | 6 |
| Design | OL | DB-XO | DB-XO | DB-PG | DB-PG | DB-PG | DB-PG | DB-PG | OL |
| RX Sessions | 1 | 2* | 2* | 1 | 1 | 1 | 1 | 1 | 1 |
| Dose/ Pressure | 0.5 mg/ 20 bar | 0.25 mg/ 20 bar | 0.5 mg/ 20 bar | 0.25 mg/ 20 bar | 0.5 mg/ 20 bar | 0.5 mg/ 20 bar | 0.5 mg/ 21 bar | 0.5 mg/ 21 bar | 0.5 mg/ 21 bar |
| | | 0.5 mg/ 20 bar | 0.5 mg/ 40 bar | 0.5 mg/ 20 bar | 0.5 mg/ 40 bar | 20 bar/ PBO | 21 bar/ PBO | 21 bar/ PBO | |
| | | 0.5 mg/ 40 bar | 20 bar/ PBO | 20 bar/ PBO | 20 bar/ PBO | | | | |
| | | 20 bar/ PBO | 40 bar/ PBO | | 40 bar/ PBO | | | | |
| | | 40 bar/ PBO | | | | | | | |

VP=venipuncture, IV=IV cannulation, ACF=antecubital fossa, BOH=back of hand

Source: Clinical reviewer

* Washout between treatment sessions ≥ 6-days

7.2.1.2 Extent of exposure (dose/duration)

Overall, a total of 1919 subjects and patients (of 2870-enrolled) received treatment with the LHM product, in 23 completed clinical studies.

Phase-1 (Early Device) Studies

Fourteen studies were conducted with early device versions (ND1, ND5, ND5.1 and ND5.2), enrolling 610-subjects (369-adult and 241-pediatric). Twelve were adult studies utilizing crossover designs, thus all adults (except one) received at least one active-LHM dose. Both pediatric studies used a parallel-group design; 162 pediatric subjects received active-LHM, while 79 received placebo. Overall, these 610-subjects received 1757 active-LHM administrations, as detailed in Table 7-22 below.

- Nine early-device studies used the ND1 early prototype, 7 in adults and 2 in children (ages 4 – 14)
- Five early-device studies were completed with the later ND5 series, all in adults.

Table 7-22 and Table 7-23 below summarize exposure in early-device studies.

Table 7-22: Early-Device Drug Exposure, by Study and by Population

| Study | Device | N | N LHM-Exposed | LHM Admins. | Placebo Admins. | Mannitol Admins. |
|--------------------------|--------|------------------------|------------------------|-------------|-----------------|------------------|
| Adult Studies | | | | | | |
| C96-101-01 | ND1 | 14 | 14 | 28 | 14 | 0 |
| DPJ 01-001 ^a | ND1 | 18 | 12 | 104 | 0 | 58 |
| DPJ 01-002 ^a | ND1 | 40 | 40 | 40 | 0 | 40 |
| MDS-20643 | ND1 | 20 | 20 | 40 | 40 | 0 |
| ICR-012770 ^a | ND1 | 18 | 18 | 199 | 0 | 199 |
| DPJ 01-003 ^a | ND1 | 30 | 30 | 147 | 0 | 147 |
| D4115-001-CL | ND1 | 8 | 8 | 78 | 36 | 0 |
| ICR-013727 | ND5 | 41 | 40 ^b | 79 | 81 | 0 |
| D4115-023-CL | ND5.1 | 40 | 40 | 320 | 320 | 0 |
| DPJ LID 009 | ND5.2 | 20 | 20 | 60 | 20 | 0 |
| DPJ 01-004 | ND5.2 | 40 | 40 | 160 | 80 | 0 |
| DPJ 01-005 | ND5.2 | 80 | 80 | 340 | 100 | 0 |
| Total Adult | | 369^b | 368^b | 1595 | 691 | 444 |
| Pediatric Studies | | | | | | |
| ICR-031086 | ND1 | 131 | 87 | 87 | 44 | NA |
| ICR-031091 | ND1 | 110 | 75 | 75 | 35 | NA |
| Total Pediatric | | 241 | 162 | 162 | 79 | NA |
| TOTAL | | 610 | 530 | 1757 | 770 | 444 |

^a Crossover studies in which subjects received both LHM and Mannitol ± PBO

^b 368 of 369-subjects received LHM – there was one device malfunction in Study-013727

Source: Table-3, Section 2.2.3, Module 2.7, Developmental Studies Summary

Table 7-23: Number of Subjects in Each Dose/Pressure Group, by Study (Early-Devices)

| Study | N | Lidocaine | | | Placebo | | |
|-------------------------|------------|----------------------|------------------------|-----------------------|-------------|------------|------------------------|
| | | 0.5-mg/ 20-25-bar | > 0.5-mg/ 20-25-bar | > 0.5-mg/ > 25-bar | 20 - 25-bar | > 25-bar | ± Mannitol > 25-bar |
| Adult | | | | | | | |
| C96-101-01 | 14 | -- | -- | 14 | -- | -- | |
| DPJ 01-001 ^a | 18 | -- | -- | 18 | -- | 18 | |
| DPJ 01-002 ^a | 40 | -- | -- | 40 | -- | 40 | |
| MDS-20643 | 20 | -- | -- | 20 | -- | -- | |
| ICR-012770 ^a | 18 | -- | -- | 18 | -- | 18 | |
| DPJ 01-003 ^a | 30 | -- | -- | 30 | -- | 30 | |
| D4115-001-CL | 8 | -- | -- | 8 | -- | -- | |
| ICR-013727 | 41 | -- | -- | 41 | -- | -- | |
| D4115-023-CL | 40 | -- | -- | 40 | -- | -- | |
| DPJ EID 0q9 | 20 | 10 | 20 | 10 | -- | -- | |
| DPJ 01-004 | 40 | -- | 40 | -- | 40 | -- | |
| DPJ 01-005 | 80 | 50 | 50 | -- | 80 | -- | |
| Total Adult | 369 | 60 | 110 | 238 | 140 | 106 | |
| Pediatric | | | | | | | |
| ICR-031086 | 131 | -- | -- | 87 | -- | 44 | |
| ICR-031091 | 110 | -- | -- | 75 | -- | 35 | |
| Total Pediatric | 241 | -- | -- | 162 | -- | -- | |
| TOTAL | 610 | 60 | 110 | 400 | 140 | 106 | |

^a Crossover studies in which subjects received both LHM and Mannitol/PBO
 Source: Table-3, Section 2.2.3, Module 2.7, Developmental Studies Summary

Phase-2/3 Studies (ND5.3 and ND5.3A Devices)

Two-thousand, two-hundred and sixty (N=2260) subjects enrolled in the nine studies conducted with either the intended commercial device (ND5.3A), or the final prototype device (ND5.3). Most late-device exposure occurred in single-dose studies.

- Pediatric studies enrolled 1761 subjects, while adult enrollment was 499 subjects
- 1389 subjects received active-LHM (single lidocaine dose; 0.50-mg for 1255, and 0.25-mg for 134)
- 274 adults received two single-dose, active-LHM exposures; 6 received four SD exposures
- Studies using the ND5.3A (final) device enrolled 1120 pediatric subjects
- Studies using the ND5.3 device enrolled 1140 subjects, both adult and pediatric

The five pediatric studies (401-001, 400-001, 002-001, 003-1, and 004-1) all utilized a parallel group design; subjects received either active drug or placebo; 906 received LHM while 855 received placebo.

The two adult trials (100-001 and 102-001) utilized a crossover design; each subject received LHM once and placebo once. Most subjects received single-doses of both active-LHM and of placebo. Of 499 adults (including replacement subjects), 476 received active-LHM, while 420 received placebo.

Open-label Study 101-001 was a safety/PK study, in which all 38 adults received single-dose, active-drug. Open-label Study 005-1 enrolled six adults, all of whom received active drug, in an assessment of product sound emission characteristics.

Anesiva counts a total of 2671 “unique dose exposures” in the ND5.3A and ND5.3 studies (adult and pediatric); of these, 1,389 were exposures to active treatment and 1,282 to placebo.

- Anesiva’s exposure tables count subjects participating in the two adult crossover studies (1-100-001 and 1-102-001) once for each “unique dose exposure.”
- In contrast, the six subjects participating in Study 1-005-1 were “... each counted once for unique dose exposure, because each was exposed four times to the same dose of active treatment.”

Of the 2671 unique exposures, 2096 delivered either lidocaine 0.50-mg or placebo at 20/21 bar; 1031 lidocaine and 1065 placebo. About 22% of unique dose exposures (575/2671) were to dose/pressure configurations different from the final (0.50-mg/20 or 21-bar).

Two subjects enrolled in more than one study. Subjects 3-003-1-1027 (active) and 3-003-1-3111 (placebo) from study 3268-3-003-1 had both previously enrolled as subjects 2-002-1-4002 (active) and 2-002-1-3066 (active) in Study 2-002-1. One subject enrolled in study 2-002-1 twice, as subject number-1011 (placebo) and as subject number-1053 (active). For these three subjects, Anesiva counted each device administration as a unique exposure.

Table 7-24 below summarizes unique exposures in the late-device studies, by those occurring in the four adult vs. five pediatric trials, and by those occurring in studies evaluating the ND5.3 vs. ND5.3A devices. Nearly two-thirds of unique exposures (1761/2,671, 65.9%) occurred in pediatric studies. Table 7-25 breaks down late-device exposure by individual study.

Table 7-24: Late-Device Exposure, by Device Version and Population (ITT Population)

| Study | 0.25mg/ 20bar | 0.5mg/ 20bar | 0.5mg/ 40bar | LHM Total | PBO/ 20 bar | PBO/ 40 bar | PBO Total | Treated Total |
|---------------------------|------------------|-----------------|-----------------|--------------|----------------|----------------|--------------|------------------|
| All 9-Studies | 134 | 1031 | 224 | 1389 | 1065 | 217 | 1282 | 2260 |
| Pediatric | 48 | 809 | 49 | 906 | 806 | 49 | 855 | 1761 |
| Adult | 86 | 222 | 175 | 483 | 259 | 168 | 427 | 499 |
| ND5.3A | - | 567 | - | 567 | 553 | - | 553 | 1120 |
| ND5.3 | 134 | 464 | 224 | 822 | 512 | 217 | 729 | 1140 |
| Both Pivotal ^a | - | 561 | - | 561 | 553 | - | 553 | 1114 |

^a Pediatric exposure only in the two-pivotal studies

Source: ISS Table 2.7.4.1.3 and dataset _____

Table 7-25: Late-Device Exposure by Study (ITT Population)

| Study | 0.25mg/ 20bar | 0.5mg/ 20bar | 0.5mg/ 40bar | LHM Total | PBO/ 20 bar | PBO/ 40 bar | PBO Total | Treated Total |
|--------------|------------------|-----------------|-----------------|--------------|----------------|----------------|--------------|------------------|
| 1-101-001 | - | 38 | - | 38 | - | - | - | 38 |
| 1-100-001 | 86 | 89 | 86 | 261 | 177 | 83 | 260 | 272 |
| 1-102-001 | - | 89 | 89 | 178 | 82 | 85 | 167 | 183 |
| 4-401-001 | 48 | 48 | - | 96 | 49 | - | 49 | 145 |
| 4-400-001 | - | 48 | 49 | 97 | 49 | 49 | 98 | 195 |
| 2-002-1 | - | 152 | - | 152 | 155 | - | 155 | 307 |
| 3-003-1 | - | 292 | - | 292 | 287 | - | 287 | 579 |
| 3-004-1 | - | 269 | - | 269 | 266 | - | 266 | 535 |
| 1-005-1 | - | 6 | - | 6 | - | - | - | 6 |
| Total | 134 | 1031 | 224 | 1389 | 1065 | 217 | 1282 | 2260 |

Source: ISS Table 2.7.4.1.2 and ISS dataset demog-d.xpt

Anesiva presented most summarized exposure data, by number of unique subjects/patients treated, rather than by single doses administered. This approach allows for acceptable assessment of product exposure, and predicted toxicity, though, because:

- Most subjects in the late-device trials, did receive only one active-drug dose
- All subjects in the two (pediatric) efficacy studies conducted with the final device received only one active-drug dose
- The proposed label clearly states that the product is intended for single-dose application only
- Product cost will likely limit actual clinical use, to single-dose application

7.2.1.3 Demographics

Age, race, and gender were recorded for all subjects in all studies. Categories of race were not identical in all studies, but were mapped as shown in Table 7-26 below.

Table 7-26: Racial Categories in Integrated Analyses

| Category in Analyses | Racial Categories in Individual Studies |
|----------------------|--|
| Caucasian | Caucasian and White |
| African American | African American and Black |
| Oriental | Oriental (specify) and Asian (specify) |
| Other | Hawaiian, Pacific Islander, Alaskan, Hispanic, Native American |

Aggregate descriptive statistics for the early device studies were not presented in the initial submission. These data were ultimately summarized, however, as presented in Table 7-27 below.

Table 7-27: Demographic Characteristics, Early-Device Studies (ITT Population)

| Characteristic | Adult | and | Pediatric | Adult | and | Pediatric |
|--------------------|----------------------------------|------------------------------------|----------------------------------|------------------------------------|----------------------------------|----------------------------------|
| | 0.5-mg/ 20-25 bar N=60 (%) | >0.5-mg/ 20-25-bar N=110 (%) | >0.5-mg/ >25-bar N=400 (%) | Placebo/ 20-25-bar N=140 (%) | Placebo/ >25-bar N=202 (%) | Mannitol >25-bar N=106 (%) |
| Gender | | | | | | |
| Male (%) | 34 (56.7) | 55 (50.0) | 236 (59.0) | 73 (52.1) | 104 (51.5) | 79 (74.5) |
| Female (%) | 26 (43.3) | 55 (50.0) | 164 (41.0) | 67 (47.9) | 98 (58.5) | 27 (25.5) |
| Age (years) | | | | | | |
| Mean ± SD | 38.6 ± 10.1 | 39.9 ± 13.4 | 25.4 ± 16.7 | 40.2 ± 12.8 | 23.6 ± 15.1 | 40.2 ± 13.3 |
| Range | 18 - 62 | 19 -65 | 4 -65 | 18 -65 | 4 -63 | 18 -65 |
| 3-7 | 0 | 0 | 43 (11.0) | 0 | 30 (14.9) | 0 |
| 8-12 | 0 | 0 | 102 (26.0) | 0 | 41 (20.2) | 0 |
| 13-18 | 1 (2.0) | 0 | 23 (5.8) | 1 (1.0) | 11 (5.4) | 3 (2.8) |
| 19-44 | 42 (70.0) | 68 (61.8) | 159 (39.8) | 86 (61.4) | 94 (46.5) | 58 (54.7) |
| 45-65 | 17 (28.3) | 42 (38.1) | 71 (17.8) | 53 (37.9) | 24 (11.9) | 42 (42.5) |
| >65 | 0 | 0 | 0 | 0 | 0 | 0 |
| Missing | 0 | 0 | 2 (1.0%) | 0 | 2 (1.0%) | 0 |
| Ethnicity | | | | | | |
| Caucasian | 56 (93.3) | 106 (96.3) | 372 (93) | 135 (96) | 174 (86) | 106 (100) |
| Other | 4 (7) | 4 (4) | 28 (7) | 5 (4) | 28 (14) | 0 |

Source: NDA Amendment-007, Tables 7.1 and 7.2, pages 12-14

Anesiva's pediatric studies included subjects up to 18 years of age, as shown below.

Table 7-28: Late-Device Studies, Enrollment of 17 and 18 Year-Olds

| Study | Population | Age-17 (N) | Age-18 (N) | Ages 17-18 (N) |
|-------------------------|------------|------------|------------|----------------|
| 2-002-1 | Pediatric | 14 | 4 | 18 |
| 3-003-1 | Pediatric | 27 | 17 | 44 |
| 3-004-1 | Pediatric | 31 | 13 | 44 |
| 4-400-001 | Pediatric | 12 | -- | 12 |
| 4-401-001 | Pediatric | 8 | 1 | 9 |
| Total Pediatric Studies | | 92 | 35 | 127 |
| 1-100-001 | Adult | -- | 4 | 4 |
| 1-102-001 | Adult | -- | 3 | 3 |
| Total All Studies | | 92 | 42 | 134 |

Source: Clinical reviewer

Table 7-29 presents demographic data for all subjects in late-device studies. Overall:

- Male and female enrollment was roughly equivalent (male 51.6%, female 48.4%).
 - The mean age was 15.8 years (\pm 12.5 SD)
 - 24.7% were aged 3–7 years
 - 25.2% were aged 8–12 years
 - 28.3% were aged 13–18 years
 - 21.8% were over 18 years
 - 0.3% were 65 years of age or older
 - The majority of subjects were Caucasian (83.4%),
 - 10.2% of subjects were African American, 4.7% were “Other,” and 1.6% were Asian
- None of these characteristics differed substantially between treatment groups.

Table 7-29: Demographic Characteristics, ND5.3A and ND5.3 Studies (ITT Population)

| Characteristic | Adult and Pediatric | | | Adult Only | | |
|--------------------|---------------------|-----------------------|-------------------|------------------|----------------------|-----------------|
| | LHM N=1389 (%) | Placebo N=1282 (%) | All N=2260 (%) | LHM N=483 (%) | Placebo N=427 (%) | All N=499(%) |
| Gender | | | | | | |
| Male (%) | 736 (53.0) | 663 (51.7) | 1166 (51.6) | 271 (56.1) | 240 (56.2) | 278 (55.7) |
| Female (%) | 653 (47.0) | 619 (48.3) | 1094 (48.4) | 212 (43.9) | 187 (43.8) | 221 (44.3) |
| Age (years) | | | | | | |
| Mean \pm SD | 18.9 \pm 14.5 | 18.6 \pm 14.4 | 15.8 \pm 12.5 | 35.0 \pm 13.0 | 35.1 \pm 13.1 | 35.1 \pm 13.1 |
| Range | 3-75 | 3-75 | 3-75 | 18-75 | 18-75 | 18-75 |
| 3-7 | 287 (20.7) | 271 (21.1) | 558 (24.7) | NA | NA | NA |
| 8-12 | 290 (20.9) | 280 (21.8) | 570 (25.2) | NA | NA | NA |
| 13-18 | 336 (24.2) | 311 (24.3) | 640 (28.3) | NA | NA | NA |
| 19-44 | 357 (25.7) | 312 (24.3) | 369 (16.3) | 357 (73.9) | 312 (73.1) | 369 (73.9) |
| 45-65 | 112 (8.1) | 102 (8.0) | 116 (5.1) | 112 (23.2) | 102 (23.9) | 116 (23.2) |
| >65 | 7 (0.5) | 6 (0.5) | 7 (0.3) | 7 (1.4) | 6 (1.4) | 7 (1.4) |
| Ethnicity | | | | | | |
| Caucasian | 1187 (85.5) | 1058 (82.5) | 1885 (83.4) | 423 (87.6) | 373 (87.4) | 436 (87.4) |
| Black | 126 (9.1) | 129 (10.1) | 231 (10.2) | 32 (6.6) | 25 (5.9) | 33 (6.6) |
| Asian | 21 (1.5) | 25 (2.0) | 37 (1.6) | 9 (1.9) | 9 (2.1) | 9 (1.8) |
| Other | 55 (4.0) | 70 (5.5) | 107 (4.7) | 19 (3.9) | 20 (4.7) | 21 (4.2) |

Source: ISS Table 2.4.7, page-28 and ISS dataset DEMOG-D.XPT

Table 7-30 on page-62 presents pediatric demographic characteristics separately Overall, in the two studies (3-003-1 and 3-004-1) conducted with the final device formulation (ND5.3A):

- Male and female enrollment was equal (557 each).
- The mean age was 10.6 years (\pm 4.3 SD), with more older than younger subjects
 - Enrollment was 38%, 32% and 31% for subjects ages 13 to 18, 8 to 12 and 3 to 7, respectively
- The majority of subjects were Caucasian (76.0%, 847/1114)
 - 14.5% of subjects were African American, 7.2% were “Other,” and 2.3% were Asian

Table 7-30: Pediatric Demographic Characteristics, ND5.3A and ND5.3 Studies (ITT Population)

| Characteristic | Pediatric | N5.3 and | N5.3A | Pediatric | N5.3A | Only |
|--------------------|------------------|----------------------|-------------------|------------------|----------------------|-------------------|
| | LHM N=906 (%) | Placebo N=855 (%) | All N=1761 (%) | LHM N=561 (%) | Placebo N=553 (%) | All N=1114 (%) |
| Gender | | | | | | |
| Male (%) | 465 (51.3) | 423 (49.5) | 888 (50.4) | 277 (49.4) | 280 (50.6) | 557 (50.0) |
| Female (%) | 441 (48.7) | 432 (50.5) | 873 (49.6) | 284 (50.6) | 273 (49.4) | 557 (50.0) |
| Age (years) | | | | | | |
| Mean ± SD | 10.4 ± 4.3 | 10.3 ± 4.3 | 10.3 ± 4.3 | 10.6 ± 4.3 | 10.6 ± 4.2 | 10.6 ± 4.3 |
| Range | 3-18 | 3-18 | 3-18 | 3-18 | 3-18 | 3-18 |
| 3-7 | 287 (31.7) | 271 (31.7) | 558 (31.7) | 172 (30.7) | 168 (30.4) | 340 (30.5) |
| 8-12 | 290 (32.0) | 280 (32.7) | 570 (32.4) | 175 (31.2) | 179 (32.4) | 354 (31.8) |
| 13-18 | 329 (36.3) | 304 (35.6) | 633 (35.9) | 214 (38.1) | 206 (37.3) | 420 (37.7) |
| Ethnicity | | | | | | |
| Caucasian | 764 (84.3) | 685 (80.1) | 1449 (82.3) | 442 (78.8) | 405 (73.2) | 847 (76.0) |
| Black | 94 (10.4) | 104 (12.2) | 198 (11.2) | 75 (13.4) | 86 (15.6) | 161 (14.5) |
| Asian | 12 (1.3) | 16 (1.9) | 28 (1.6) | 11 (2.0) | 15 (2.7) | 26 (2.3) |
| Other | 36 (4.0) | 50 (5.8) | 86 (4.9) | 35 (5.9) | 47 (8.5) | 80 (7.2) |

Source: ISS Table 2.4.9, page-31.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary clinical sources were used to evaluate product safety.

7.2.2.1 Other studies

The only clinical trial data reviewed were those submitted to application 22-114, and its first review cycle amendments.

7.2.2.2 Postmarketing experience

Zingo™ has not been approved, in the USA or elsewhere, nor have similar products (pressurized dermal delivery of local anesthetic).

7.2.2.3 Literature

To support product safety claims, the applicant relied, in part, on findings cited in 37-articles and book chapters published in the (peer-reviewed) literature. The literature search appears to have been appropriate and adequate, containing the information necessary to evaluate previous human experience with topical and intradermal lidocaine and other local anesthetics.

7.2.3 Adequacy of Overall Clinical Experience

[See Section 7.2.1 above for details regarding the extent of product exposure.]

Overall pediatric exposure was sufficient to support a finding of safety for single-dose pediatric use for the proposed indication. These pediatric findings can likely be extrapolated to support the safety of single-dose use, for the same indication, in the healthy, non-elderly, adult population; the skin in pediatric subjects is more vulnerable to acute topical drug-induced injury than that in adults. Exposure in the elderly population was insufficient; only seven subjects ≥65 were treated in late-device trials.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The Pharmacology/Toxicology review team considers the special animal testing conducted to have been adequate. Specifically, the minipig dermal toxicology study was adequately designed and conducted, with findings that do not raise concerns about unrecognized potential human toxicities.

Animal / *in vitro* studies reviewed by CDRH show epidermal and dermal deposition of (non-drug) particulate matter. Penetration is not considered to be deep enough to be of concern; the small volumes deposited are quickly sloughed off.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was not called for in the late-device studies, except for pregnancy screening. Likewise, only two early-device studies required clinical laboratory testing (except for pregnancy screening). Nevertheless, given the lack of systemic exposure with single-dose use on intact skin, as proposed in the label, routine clinical testing was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No metabolic evaluation was conducted. This is acceptable, because systemic exposure is not expected with use of this product, as labeled. The only PK study conducted (1-101-001 in 38 adults) evaluated only single-dose treatment, however. Nevertheless, it is anticipated that product cost will make supra-therapeutic dosing (multiple, simultaneous product applications) clinically infeasible.

7.2.7 Adequacy of Evaluation for Potential AEs; Recommendations for Further Study

There were no studies using zero-pressure devices; all subjects were treated with pressurized helium (most at 20-21 bar). It is not possible to ascertain, from the studies conducted, whether adverse events and skin reactions may have been attributable to the delivery system/device, and not necessarily to the active drug. Controlled studies comparing AE and skin change rates between subjects treated with the 20-bar and 40-bar placebo LHM devices, and those not treated with any device, could provide useful information, but would necessitate use of a double-dummy design.

Nevertheless, adverse events and appreciable skin changes were limited both in frequency and severity, demonstrating a relatively benign safety profile.

Table 7-31: Grading Scales for Assessment of Skin Changes (Late-Device Studies)

| Grade | Erythema | Edema | Pruritus | Hemorrhage/Petechiae |
|-------|---|--|-------------|---|
| 0 | No erythema | No edema | No pruritus | None |
| 1 | Very slight erythema (barely perceptible) | Very slight edema (barely perceptible) | Occasional | Up to 5 isolated petechiae |
| 2 | Well defined erythema | Slight edema (area edges well defined by raising) | Constant | Greater than 5 isolated petechiae |
| 3 | Moderate to severe erythema | Moderate edema (raised ≈ 1-mm) | N/A | Many petechiae, with some coalescence |
| 4 | Severe erythema (beet red) to slight eschar formation | Severe edema (raised > 1 mm, extending beyond exposure area) | N/A | Numerous petechiae ± pin-prick surface blood spots, or surface bleeding |
| 5 | N/A | N/A | N/A | Frank bleeding |

Source: ISS page-7, Table-1 and page-8, Table-2

7.2.8 Assessment of Quality and Completeness of Data

Overall, the quality and completeness of the data contained in this application were adequate to assess product efficacy and safety, for the proposed indication, in the pediatric population (ages 3 to 18).

7.2.9 Additional Submissions, Including Safety Update

No 120-day safety update was submitted. Anesiva's most recent annual report (03/19/2007) states that all clinical trials initiated had been completed, and data submitted to the application. No new trials had begun subsequent to submission of the application.

Several amendments were submitted in response to requests from the review teams. These are summarized in Table 12-1 on page-125. Several requests were necessary in order to obtain integrated and summarized early-device safety data, but ultimately, the information submitted was adequate to permit a thorough safety review.

7.3 Summary of Selected Drug-Related AEs, Data Limitations, and Conclusions

Table 7-11 and Table 7-12 above summarize treatment-emergent adverse events reported during the nine late-device trials. Few differences were found, between active-device and placebo-device subjects. Where differences do exist, clinical significance is expected to be negligible.

No studies used zero-pressure devices; all subjects were treated with pressurized helium (most at 20-21 bar). It is not possible to ascertain, from the studies conducted, whether adverse events and skin reactions may have been attributable to the delivery system/device, and not necessarily to the active drug. Nevertheless, adverse events and appreciable skin changes were limited both in frequency and severity, demonstrating a relatively benign safety profile.

Safety and tolerability findings in the three (pediatric) ND5.3 studies were very similar to those in the two final-device (ND5.3A) studies, thus data were pooled across all late-device pediatric studies.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The Phase-1 data (early-device studies), were reviewed on a study-by-study basis, in part, because the application included no integrated summary of these data. Pooled safety data were reviewed for the late device studies.

7.4.1.2 Combining data

Safety data were combined separately, for the early-device and for the late-device studies. As noted above (Section 7.2.9), several requests were necessary in order to obtain integrated and summarized early-device safety data. Anesiva contended, until five months into the review, that an integrated summary of early-device safety data would be uninformative, and impractical to create, because of design, dose and pressure differences between the five early prototype devices.

Late-device study safety data were more readily combinable, because all studies (except for 1-005-1, in six male volunteers) used one of two designs:

- Randomized, double-blind, placebo-controlled, parallel group studies, in which subjects received only one treatment (active-drug, or placebo-device)
- Randomized, double-blind, placebo-controlled, within-subject crossover studies, in which subjects received both study treatments (or three treatments, in Study 1-100-001)

Where possible, pooled safety data were compared, between the late-device and early-device study populations. Within the combined late-device data, the only readily made comparisons were between pooled pediatric and pooled adult data.

Safety data were also pooled for the exploratory analyses described in Section 7.4.2. The studies combined for each of these subgroup analyses are shown in Table 7-32 below.

Table 7-32: Studies Combined for Subgroup Safety Analyses

| Study | Gender | Race | Age Group | | Device Model | | Anatomic Site | | Procedure | | |
|----------------|--------|------|-----------|-------|--------------|------|---------------|-----|-----------|----|----|
| | | | Peds | Adult | 5.3 | 5.3A | BOH | ACF | IV | VP | |
| 3268-3-003-1 | X | X | X | -- | -- | X | X | X | X | X | X |
| 3268-3-004-1 | X | X | X | -- | -- | X | X | X | X | X | X |
| 3268-1-005-1 | X | X | -- | X | -- | X | X | X | X | -- | -- |
| 3268-1-100-001 | X | X | -- | X | X | -- | -- | X | -- | -- | X |
| 3268-1-101-001 | X | X | -- | X | X | -- | -- | X | -- | -- | -- |
| 3268-1-102-001 | X | X | -- | X | X | -- | X | -- | -- | -- | X |
| 3268-4-400-001 | X | X | X | -- | X | -- | X | -- | -- | -- | X |
| 3268-4-401-001 | X | X | X | -- | X | -- | -- | X | -- | -- | X |
| 3268-2-002-1 | X | X | X | -- | X | -- | X | -- | -- | -- | X |

Source: Modified from ISS Table-29, page-74

7.4.2 Explorations for Predictive Factors

Analyses included assessment of the role of lidocaine dose, device pressure, and particle size. These findings are discussed in Section 7.1.5 above.

Because no single study enrolled both adults and children, direct comparisons between the two populations could not be made. Thus, pooled (by age group) safety data were compared, between the pediatric and adult (late-device) populations.

Subgroup analyses not described under this section's subcategories included:

- Intensity of treatment-emergent adverse events was analyzed by treatment group (active vs. placebo). There were no apparent differences.

7.4.2.1 Explorations for dose dependency for adverse findings

Increases in device pressure appeared to increase the incidence of post-treatment mild to moderate erythema. Variations in lidocaine dose did not appear to affect AE or skin change incidence, in the late-device trials. These trials, however, evaluated only two doses; 0.25-mg and 0.50-mg.

In Study 031091 administration site adverse events were more common at the ACF site than the BOH site and the severity appeared to be greater at 40 bar than at 30 bar.

7.4.2.2 Explorations for time dependency for adverse findings

Anesiva's shift analyses for skin assessment findings show that nearly all treatment-site skin changes occurred within two-hours of treatment; most within 15 to 20 minutes of treatment (Tables 4.3.1 to 4.3.4 in ISS Appendix, Section 16). Most skin abnormalities meeting AE criteria also occurred shortly after treatment. Overall, only three delayed (>3-hours) reactions occurred; two in active drug treated, and one in a placebo-treated subject).

7.4.2.3 Explorations for drug-demographic interactions

The overall proportion of subjects with AEs was slightly lower in pediatric subjects than in adult subjects (9.2% vs. 10.4%). In both age groups, however, incidence and types of adverse events were similar between active-drug and placebo treated subjects. It should be noted, also, that several of the late-device pediatric trials enrolled hospitalized children with acute and chronic diseases.

The only differences >1% in AE incidence, between active and placebo treated adults, were:

- "Venipuncture site hemorrhage" (n=3 active (0.6%), and n=13 placebo (3.0%))
- "Dizziness" (n=6 active (1.2%), and n=1 placebo (0.2%))

There were no apparent differences between genders, in TEAE rates, or in abnormal skin assessments.

Racial differences in observed skin site abnormalities (as assessed) are most likely, to some extent, related to masking of erythema and petechiae by darker skin in African-Americans. In active-drug treated subjects, lower percentages of African-Americans had abnormal erythema or hemorrhage/petechiae, compared with Caucasians (34.3% vs. 53.2%, and 52.1% vs. 75.4%, respectively).

The overall frequency of adverse events in active-drug treated subjects, was higher in African-Americans, 13.4% (n = 31) compared to Asians, 2.7% (n=1), and to Caucasians, 9.3% (n=175). Within each race category, however, the incidence and nature of adverse events was generally similar between the active and placebo treatment arms.

AEs with incidence differences >1%, between active and placebo treated AA subjects were:

- "Pruritis" (n=3 active (2.4%), and n=0 placebo)
- "Tachypnea" (n=2 active (1.6%), and n=0 placebo)
- "Vomiting NOS" (n=2 active (1.6%), and n=4 placebo (3.1%))
- "Headache" (n=0 active, and n=3 placebo (2.3%))

AEs with incidence differences >1%, between active and placebo treated Asian subjects were:

- "Venipuncture site bruise" (n=0 active, and n=1 placebo (4.0%))

AEs with incidence differences >1%, between active and placebo treated Caucasian subjects were:

- "Venipuncture site hemorrhage" (n=2 active (0.2%), and n=13 placebo (1.2%))

7.4.2.4 Explorations for drug-disease interactions

Not possible given the available data.

7.4.2.5 Explorations for drug-drug interactions

Not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Anesiva states that because of the lack of systemic absorption shown in PK Study 1-101-001, and the local site of action, correlations of systemic levels with effect size were not used for dose selection. The doses evaluated in late-device trials were "... determined by safety data from early development studies." Two of the four late-device dose-ranging trials included a 0.25-mg treatment arm, a dose lower than any tested in the early-device trials (Table 8-1).

The highest lidocaine dose administered, 5.0-mg, was administered in only one study, DJP-01-001 (2-mg, 3-mg and 5-mg, at 20-bar and 40-bar.) Otherwise, the early device studies evaluated 0.25-mg to 3.0-mg lidocaine doses (at 20-bar to 60-bar), with most including the 3.0-mg dose. Both pediatric early device studies administered 3.0-mg lidocaine doses at 30-bar and at 40-bar. The last four early-device studies evaluated lidocaine doses ranging from 0.50-mg to 3.0-mg (at 20 to 30-bar).

Table 8-1: Doses and Pressures Evaluated, Early-Device Trials and Late-Device Dose-Ranging

| Study | Device | N | Doses (mg) | Pressures (bar) | Particle Size (µm) | Treatments ^a /Subject |
|-------------------------|--------|-----|------------|-----------------|--------------------|----------------------------------|
| C96-101-01 | ND1 | 14 | 3 | 30 | -- | 1 |
| DPJ 01-001 ^a | ND1 | 18 | 2, 3, 5 | 40, 60 | -- | 4 |
| DPJ 01-002 ^a | ND1 | 40 | 3 | 40 | -- | 1 |
| MDS-20643 | ND1 | 20 | 3 | 40 | -- | 2 |
| ICR-012770 ^a | ND1 | 18 | 3 | 40, 60, 80 | -- | 3 |
| DPJ 01-003 | ND1 | 30 | 3 | 40, 50, 60 | -- | 3 |
| D4115-001-CL | ND1 | 8 | 3 | 40 | -- | 3 |
| ICR-013727 | ND5 | 41 | 3 | 30 | -- | 1 |
| ICR-031091 ^b | ND1 | 116 | 3 | 30, 40 | <38, 38-53 | 1 |
| ICR-031086 ^b | ND1 | 132 | 3 | 30, 40 | <38, 38-53 | 1 |
| D4115-023-CL | ND5.1 | 40 | 3 | 30 | 10, 20 | 2 |
| DPJ LID 009 | ND5.2 | 20 | 0.50, 1, 2 | 20, 25, 30 | -- | 1 |
| DPJ 01-004 | ND5.2 | 40 | 3 | 20 | -- | 1 |
| DPJ 01-005 | ND5.2 | 80 | 0.50, 1 | 20, 25 | 30, 40 | 2 |
| 1-100-1 | ND5.3 | 272 | 0.25, 0.50 | 20, 40 | 35 | 2 |
| 1-102-1 | ND5.3 | 183 | 0.50 | 20, 40 | 35 | 2 |
| 4-401-1 ^b | ND5.3 | 145 | 0.25, 0.50 | 20 | 35 | 1 |
| 4-400-1 ^b | ND5.3 | 195 | 0.50 | 20, 40 | 35 | 1 |

^a One or more active-drug doses, with at least one placebo dose

^b Pediatric

Source: Clinical reviewer

In Study 4-401-001, efficacy of the 0.5 mg/20-bar and 0.25 mg/20-bar doses were not statistically different. "However, the effect size was numerically greater for the 0.5 mg/20 bar dose in both the primary analyses."

8.2 Drug-Drug Interactions

Drug-drug interaction studies were not considered necessary, given the lack of systemic absorption expected with labeled (and also with feasible) product use.

8.3 Special Populations

Geriatric subjects were not well represented in the safety database. Only seven subjects older than 65 years received study drug. The Zingo™ product's safety profile could possibly be different for geriatric patients, because of age-related alterations in skin integrity. Efficacy differences, though theoretically possible, are not expected, however.

Given the lack of systemic absorption with labeled and with anticipated product use, alterations in dosing instructions would not be necessary for patients with renal or hepatic impairment.

8.4 Pediatrics

Most subjects studied were pediatric aged.

8.5 Advisory Committee Meeting

An advisory committee meeting was not considered to be necessary.

8.6 Literature Review

No additional review of the literature was undertaken for this review.

8.7 Postmarketing Risk Management Plan

No need for postmarketing risk management is anticipated.

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On Original**

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy

The application provides adequate support of the product's efficacy, and substantial evidence for its safety, for the proposed indication (in 3 through 18 year-olds). Both studies conducted with the final, to-be-marketed device, yielded supportive efficacy findings, but enrolled only pediatric subjects. Only two (of seven) controlled late-device studies enrolled adults, however.

The proposed label requires substantial revision, largely because of implied and other unacceptable efficacy and τ claims. These claims are, for the most part, based upon statistical analyses (of secondary efficacy data) of questionable appropriateness and rigor.

b(4)

The results of the primary efficacy analyses (ITT) for Studies 3-003-1 and 3-004-1 are shown below.

Table 9-1: Final Device Studies, Modified Wong-Baker FACES Score

| ITT Populations | Study 3-003-1 | | Study 3-004-1 | |
|-------------------------|------------------|----------------------|------------------|----------------------|
| | LHM (N = 292) | Placebo (N = 287) | LHM (N = 269) | Placebo (N = 266) |
| Adjusted Mean, LSM | 1.77 | 2.10 | 1.38 | 1.77 |
| Standard Error of LSM | 0.09 | 0.09 | 0.09 | 0.09 |
| Difference in LSMs (SE) | -0.33 (0.13) | | -0.39 (0.13) | |
| p-value | 0.011 | | 0.003 | |
| 95% Confidence Limits | -0.58, -0.08 | | -0.65, -0.13 | |

Source: Study 3-003-1 Tables 11.1.10 and 5.1.1B, Study 3-004-1 Tables 11.1.10 and 5.1.1B in Section-14

In both studies, treatment with active drug resulted in statistically significantly less pain, from venipuncture or IV cannulation, compared with placebo. Effect sizes were rather small, however.

Treatment with LHM resulted in statistically significantly ($p = 0.011$) less pain, from venipuncture or IV cannulation, compared with placebo, in both studies. Effect sizes were rather small, however.

Secondary efficacy findings from these trials, and primary and secondary findings from the ND5.3 trials, are generally supportive.

Safety

Zingo™ was shown to be safe and well tolerated across five pediatric and four adult studies conducted with the ND5.3A and ND5.3 devices. Safety was shown in the target (pediatric) population using the final commercial device (ND5.3A). The overall pediatric population included a large number of patients with acute and chronic medical conditions such as solid organ transplantation and juvenile rheumatoid arthritis, as well as those undergoing major and minor surgical procedures and invasive diagnostic tests. The pediatric safety reflects likely reflect anticipated clinical use of the product.

Adverse events were mostly local to the treatment site, mild, and self-limited, resolving without treatment. AEs frequency and pattern were similar between active-drug and placebo-treated subjects.

SAEs and severe skin reactions were very rare. Of the late-device pediatric subjects, 1.0% (9/809) developed serious or severe treatment site reactions (Grade-4 (n=8) or Grade-5 (n=1) hemorrhage/petechiae)). Two were pediatric post-transplant patients, chronically on glucocorticoids. Another two had “juvenile chronic arthritis” treated with methotrexate. In both cases the subjects’ condition improved spontaneously within two hours, with complete resolution within 48 hours.

Three adult subjects (3/499, 0.6%) treated with high pressure devices (ND5.3, 0.5 mg/40 bar) also developed Grade 4 (n = 2) or Grade 5 (n = 1) hemorrhage/petechiae following Zingo™ treatment.

Error! Reference source not found. Error! Reference source not found. summarizes TEAE incidence rates in the early-device studies, by WHO-ART SOC and treatment group. AE PTs reported in $\geq 0.5\%$ of subjects in any treatment group are listed.

- Most AEs were localized to the treatment site, regardless of treatment condition
- Overall AE incidence, and treatment site related AE incidence were comparable between subjects treated with 0.50-mg/20-25-bar devices, and placebo/20-25-bar devices.
- In both active-drug and placebo-device treated subjects, “Application site disorders” occurred more frequently with higher device pressure (>25-bar)
 - It is not possible, however, to assess the relative roles of increases in device pressure, and increases in lidocaine dose; the >25-bar devices only administered lidocaine doses >0.50-mg
 - Several PTs within this SOC, though, were actually more frequent with 20-25 bar devices than with devices >25-bar (i.e., injection site bruising, injection site bleeding)
- Differences between treatment groups in PT incidence rates are likely attributable, at least in part, to small numbers of patients within each treatment group, and overall low AE frequency

Systemic lidocaine exposure is not expected.

Laboratory and vital sign were not collected in most trials, thus are non-informative.

9.2 Recommendation on Regulatory Action

I recommend approval for NDA 22-114, for the pediatric population (ages 3 through 18), for the proposed indication, “...for use on intact skin to provide local analgesia prior to venipuncture or intravenous cannulation.”

9.3 Recommendation on Postmarketing Actions

None

9.4 Labeling Review

See Section 11.

9.5 Comments to Applicant

The applicant should be urged to enroll adequate numbers of geriatric aged subjects in their upcoming adult efficacy trials.

10 APPENDIX ONE: REVIEW OF INDIVIDUAL STUDY REPORTS

10.1 Study 3-003-1

A Phase III, Randomized, Double-Blind, Placebo-Controlled Study to Confirm the Effectiveness and Safety of ALGRX 3268 in Pediatric Subjects

[Note: Identical to Study 3-004-1 (Section 0) in design, population, efficacy measures and planned analyses]

10.1.1 Findings vs. Labeling Claims

The Study 3-003-1 efficacy findings support the Applicant's efficacy claim for the proposed indication. Subjects treated with Zingo™ one to three minutes prior to venipuncture or intravenous cannulation, reported less procedure-related pain than those treated with placebo.

10.1.2 Study Plan

The initial version of Protocol 3-003-1 was dated 10/14/2004. Three amendments were implemented; two prior to initiation of study enrollment, and one after (See Section 10.1.8 below). The Statistical Analysis Plan was dated 10/02/2005 and revised 09/30/2005. (Database lock was 10/05/2005.)

10.1.3 Objectives, Design and Population

10.1.3.1 Objectives

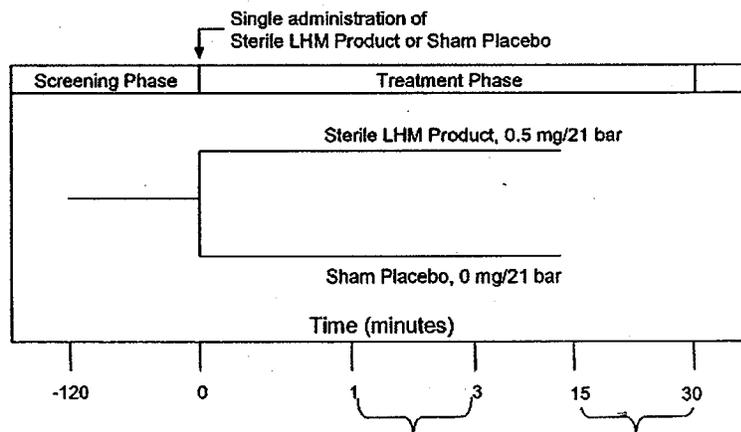
The protocol-specified primary objective of Study 3-003-1 was "To confirm the efficacy of ALGRX3268 compared to placebo in pediatric subjects."

The protocol-specified secondary objective was "To confirm the safety and tolerability of ALGRX3268 compared to placebo in pediatric subjects."

10.1.3.2 Design

Study 3-003-1 was designed as a multi-center, randomized, DB-PC, parallel-group, single-dose study, in pediatric subjects undergoing (medically necessary) venipuncture or peripheral venous cannulation at the antecubital fossa or back of hand. Figure 10-1 below diagrams the study design.

Figure 10-1: Study 3-003-1 Design – Treatment and Assessment Schedule



Minute (-120)

- Informed consent, Demographics, Reason for procedure, Inclusion/Exclusion criteria, Concomitant medications, Parent assessment of child's perception of anticipated pain of procedure
- Randomization if eligible

Minute (Zero)

- Study drug administration
- Dermal assessment of drug administration site (immediately before and after dosing)
- AEs, Concomitant medication

Minute (+1)

- Venipuncture or peripheral venous cannulation (pain model)

Minutes (+1) to (+3)

- Child scores pain (Wong-Baker FACES for all + 100-mm VAS for ages 8 – 18))
- Parent scores child's pain (100-mm VAS)
- Investigator categorizes procedure (venipuncture/IV) as success or procedure
- AEs, Concomitant medications
- Dermal assessment of drug administration site

Minutes (+15) to (+30)

- Dermal assessment of drug administration site
- AEs, Concomitant medications

10.1.3.3 Population

Five hundred and four (N=504) pediatric subjects, ages three through eighteen, scheduled to undergo venipuncture or peripheral venous cannulation, were to be enrolled.

Inclusion criteria were to be:

1. Children of either gender who are to undergo venipuncture or peripheral venous cannulation at the antecubital fossa or the back of the hand.
2. Ages 3 to 18 inclusive; grouped as 3 to 7 years, 8 to 12 years, and 13 to 18 years.
3. Children must have sufficient cognitive skills to identify faces depicting extremes of pain on the Wong-Baker FACES pain rating scale (the FACES scale; ages 3-18) and the extremes of pain on a 100 mm visual analog scale (VAS; ages 8-18).
4. Consent forms must be approved by the appropriate IRBs. Signed informed consent must be granted by the parent/legal guardian and assent to participate should be sought (either verbally or in writing) from each child.
5. In females who have reached menses, and who – in the judgment of the investigator or designee are sexually active – a negative urine pregnancy test must be documented prior to enrollment. A negative urine pregnancy test is required in all teenage girls who have reached menses or are over 14 years old.

Exclusion Criteria were to be:

1. Previous history of allergic reaction to any local anesthetic or tape/adhesive dressing.
2. Any medical condition or instability that in the judgment of the investigator might adversely impact the conduct of the study and the collection of data.
3. Active local infection or skin pathology at the site of venipuncture or peripheral venous cannulation.

4. Subjects with tattoos, surgical scars, ports, implantable devices or a skin condition that may interfere with product placement or skin site assessments.
5. Female subjects who are pregnant or lactating; females with a positive serum or urine pregnancy test; females of childbearing potential who are not using adequate contraception.
6. Prior participation in an ALGRX 3268 study.
7. Venipuncture or peripheral venous catheter insertion at the proposed site within the prior two weeks (longer if bruising is apparent).
8. Any child deemed uncooperative or exceptionally upset prior to study drug administration.
9. The subject has taken any investigational medication within 1 month prior to administration of study drug or is scheduled to receive an investigational drug other than ALGRX 3268 while participating in the study.

Minor deviations from entry criteria were to be "... allowed only if the investigator and the medical monitor agree in writing prior to subject enrollment.

10.1.4 Study Treatment

Randomization/Informed Consent

Each investigational site was to receive its own computer-generated randomization schedule. Distribution of subjects to active or placebo was to be in a 1:1 ratio. Every subject who signed (or whose guardian signed) the informed consent, was to be assigned a subject number, unique to Study 3-003-1. Drug administration site would be investigator-assigned, depending on clinical conditions.

Randomization was to be stratified, by site and by age group (3 to 7 years, 8 to 12 years and 13 to 18 years). Enrollment for an age group was to be discontinued when the target number had been attained. Subjects were to be approximately equally distributed across gender, within each age group.

Study Drug Treatment

Patients were to receive one of two treatments, one to three minutes prior to venipuncture or intravenous cannulation;

- Lidocaine 0.5-mg intradermally at 21-bar (35- μ m particle size)
- Placebo intradermally at 21-bar (no drug substance)

Prohibited Concomitant Medication/Therapy

"Other local anesthetic products" were not to be administered at the site of venipuncture or peripheral venous cannulation, from screening until after study completion or withdrawal. All other concomitant medications were to be recorded in the CRF.

Replacement of Subjects

Discontinuations prior to completion of the primary efficacy assessment were to be replaced. The replacement subject was to receive the same treatment as the discontinued subject. Dropouts that had received study treatment were to be included in the primary ITT analysis, and in the safety analyses. A replacement subject was to be enrolled for each discontinuation (to the same treatment arm). Subjects were to be discontinued by the investigator (and replaced) for:

- Failed initial venipuncture/IV attempts
If venipuncture or cannulation was not successful on the first attempt, subjects were to be considered "... non-evaluable due to the confounding effects of multiple needle insertions." Subjects whose venous procedure was not successful on the first attempt were to be discontinued from the study, and

replaced with another subject. Replacement subjects were each to be assigned to the same treatment arm as the originally randomized subject they would be replacing.

- Instances of device failure
- Replacement subjects were also to be assigned for each subject for which the drug delivery device failed to actuate (same treatment condition). A central facility would be responsible for assigning replacement numbers.

10.1.5 Screening Assessment

Assessments performed at screening were to include:

- Review of inclusion and exclusion criteria and elicitation of demographic data
- Documentation of the reason for the venipuncture/IV.
- Negative pregnancy tests were to be required for some, but not all female subjects. The protocol included the following instructions to investigators;
In females who have reached menses, and who – in the judgment of the investigator or designee are sexually active – a negative urine pregnancy test must be documented prior to enrollment. A negative urine pregnancy test is required in all teenage girls who have reached menses or are over 14 years old.
- Children in the 3 to 7 year age group were to be given a “seriation test,” in which they would be asked to place six triangles in size order, from smallest to largest. Children able to complete the task would be considered capable of identifying the extremes of pain depicted on the Wong-Baker FACES.

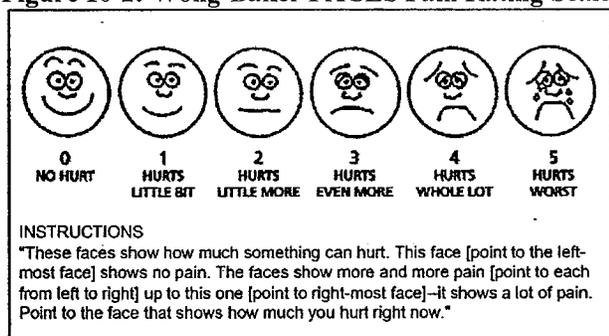
10.1.6 Efficacy Assessment

Table 10-1 below and Figure 10-1 above summarize the overall schedule for Study 3-004-1 efficacy assessment and procedures.

10.1.6.1 Primary Efficacy Measure

The primary efficacy measure, in all age groups, was to be the subject’s assessment of pain, from venipuncture or intravenous cannulation one to three minutes after study drug administration. The pain assessment instrument was to be the Wong-Baker-FACES pain rating scale, a six-point scale anchored at zero (“No Hurt”) and five (“Hurts Worst”), as shown in Figure 10-2 below.

Figure 10-2: Wong-Baker FACES Pain Rating Scale



The instructions to subjects were modified from those in the original Wong-Baker FACES instrument. Explain to the child that each face is for a person who feels happy because he has no pain (hurt) or sad because he has some or a lot of pain. Face 0 is very happy because he doesn't hurt at all. Face 1 hurts just a little bit. Face 2 hurts a little more. Face 3 hurts even more. Face 4 hurts a whole lot, but Face 5 hurts as much as you can imagine, although you don't have to be crying to feel this bad. Ask child to choose the face that best describes how he/she is feeling.

The instructions utilized throughout the Zingo™ development program were based on the Faces Pain Scale-Revised, as described and validated by Hicks.

These faces show how much something can hurt. This face [point to the left-most face] shows no pain. The faces show more and more pain [point to each from left to right]-up to this one [point to right-most face]—it shows very much pain. Point to the face that shows how much you hurt right now.

10.1.6.2 Secondary Efficacy Measures

Key secondary efficacy measures were to be subjects' assessment of pain using;

- 100-mm VAS score (0 (zero) for "No Pain" to 100 for "Extreme Pain"), for children in the middle (ages 8-12) and oldest (ages 13-18) age groups combined.
- The Wong-Baker FACES pain rating scale, analyzed separately by age group (ages 3-7, 8-12, 13-18)

Additional secondary efficacy measures were to include;

- Treatment effect size, by combining the two different pain scales using Glass's meta-analysis
- Parents' assessment of child's pain, following venipuncture/IV, measured using 100-mm VAS
- Success rate of venipuncture or peripheral venous cannulation.

Table 10-1: Study 3-003-1 Assessment and Event Schedule

| Assessment / Event | Screening (-120) Mins. | Treatment 0 Mins. | Treatment 1-3 Mins. | Treatment 15 Mins. | Treatment 30 Mins. |
|---|---------------------------|----------------------|------------------------|-----------------------|-----------------------|
| Consent / Demographics | X | | | | |
| Reason for Venipuncture/IV | X | | | | |
| Urine Pregnancy in Females ^a | X | X | | | |
| Inclusion/Exclusion Criteria | X | X | | | |
| Study Drug Administration | | X | | | |
| Venipuncture/ IV Cannulation | | | X | | |
| Efficacy Assessments | | | X | | |
| Vital Signs | | X | | | X |
| Skin Assessment, AEs | | X ^b | X | X | X |
| Concomitant Medications | X | X | X | | X |

^a "In females who have reached menses, and who – in the judgment of the investigator or designee are sexually active – a negative urine pregnancy test must be documented prior to enrollment. A negative urine pregnancy test is required in all teenage girls who have reached menses or are over 14 years old. Where the Treatment Phase immediately follows the Screening Phase on the same day, only one pregnancy test is required."

^b ACF or BOH assessed for erythema, edema, pruritus, hemorrhage or petechiae, just before and after study drug admin.

10.1.7 Statistical Analysis Plan

The Statistical Analysis Plan, dated September 02, 2005, was revised September 30, 2005. Both dates were well after enrollment had concluded, but prior to the reported database lock date, October 05, 2005.

Sample Size Calculation

The target sample size was based upon data from the earlier Study 2-002-1, in which ALGRX 3268 was administered to children ages 3-18, at the BOH. Anesiva states that the 2-002-1 results indicated that the mean WBF scores for children ages 3-12 were 1.25 and 1.91, for the active and the placebo groups, respectively. The standard deviation was 1.65. In order to detect the same pain score difference between

treatment conditions, with 90% power, using a 5% significance level (two-sided), 135-subjects per treatment group would be required.

The statistical analysis plan went on, however, to state “Therefore, 252 subjects for each treatment group will have more than 90% power for detecting a desired pain score difference. In order to insure a balanced number of 3 age groups of children, a sample size of 168 children within each age group will be randomized to either ALGRX 3268 or placebo treatment group. Therefore, a total of 504 children will be recruited in this study. In addition, this sample size will allow enough subjects to be assessed for the safety parameters. “

Analysis Populations

Efficacy analyses were to be performed on three analysis populations;

- The full analysis set, including subjects who received study treatment and had recorded results for the primary efficacy endpoint (Wong-Baker FACES) following venipuncture or IV cannulation.
 - This set was to include both originally randomized subjects and replacement subjects.
- The safety population (which is also intent-to-treat (ITT) population), including all subjects who received study drug.
- The efficacy evaluable set (per protocol), including all subjects in the full analysis set, except for subjects with major protocol violations, as determined by Anesiva prior to breaking the blind.

Analyses

Continuous variables would be summarized by the mean, median, standard deviation (SD), range and N. Categorical variables would be summarized by the frequency and percentage of subjects in each category.

A two-sided test with a significance level of 0.05 was to be used for any hypothesis testing (except for interaction testing, for which 0.10 was to be used). In addition, the 95% confidence interval was to be provided for the point estimate.

Each subject was to be categorized into one of three age groups. Summary tables were to be presented separately for each of the three age groups. All summary tables were also to be presented for all subjects combined “... to identify the treatment effect across age groups.” If a subject were randomized to an incorrect age group, their data were to be summarized and analyzed based upon the correct age group.

10.1.8 Safety Data

AEs were to be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 5.1. Concomitant medications were to be categorized using the World Health Organization Drug Reference List (WHO-Drug, no version specified).

10.1.9 Changes in Study Conduct or Planned Analyses

10.1.9.1 Protocol Amendments

There were three amendments to Protocol 3-003-1, summarized in Table 10-2 below. Two were implemented prior to enrollment; the third after only 10% of subjects had been enrolled.

Table 10-2: 3-003-1 Protocol Amendments

| No. | Date/ N Already Enrolled* | Amendment Item and Purpose |
|-----|------------------------------|--|
| 01 | 11/18/2004 N = 0 | <ol style="list-style-type: none"> 1. Incorporated wording acknowledging investigators' institutional policy with regard to pregnancy testing for teenage girls 2. Changed 'Parent assessment of child's pain' rating scale (used in 3 to 7 year-olds) from 5-point categorical to 100-mm VAS 3. Changed wording for description of '100-mm VAS Pain' secondary outcome measure; description of 100-mm anchor changed from "Extreme Pain" to "Worst Possible Pain." 4. Changed wording for description of '100-mm VAS Discomfort' secondary outcome measure; description of 100-mm anchor changed from "Extreme Discomfort" to "Worst Possible Discomfort." 5. '100-mm VAS Discomfort' secondary outcome measure; description of 100-mm anchor changed from "Extreme Discomfort" to "Worst Possible Discomfort." 6. Addition to secondary analysis plan; "the responder rate between the 2-treatment groups will be compared using a Cochran-Mantel-Haenszel (CMH) test stratifying by center." 7. 100-mmVAS secondary outcome measure; description of 100-mm anchor changed from "Extreme Pain" to "Worst Possible Pain" 8. Removed references to assessment of vital signs 9. Removed references to "Seriation test" for 3 to 7 year-olds. 10. Other minor wording revisions |
| 02 | 12/02/2004 N = 0 | <ol style="list-style-type: none"> 1. Revised study drug labeling; <ul style="list-style-type: none"> - Removed "Lot. No." and CODE NO" - Added "Age Group" and "Treatment Day" - Added "Note that the part of the label giving treatment details is blinded and will be opened only in the event of a medical emergency where there is a need to know the treatment assigned. If opened, the medical monitor MUST be notified." |
| 03 | 01/18/2005 N ≈ 57* | <ol style="list-style-type: none"> 1. Removed references to a "Coordinating Investigator" 2. Removed "Pregnancy Test" from routine screening assessments 3. Revised wording for inclusion criterion number-5 to "Female subjects who are pregnant or lactating; females with a positive serum or urine pregnancy test; females of childbearing potential who are not using adequate contraception." 4. Added "In case of a performance event (e.g., integrity of foil package has been compromised), the subject will be replaced." |

Source: Clinical reviewer from 3-003-1 Study Report Appendix 16.1.1

Total Study Enrollment = 579

10.1.9.2 Changes in the Planned Statistical Analyses

[Note: Analysis populations are defined in Section 10.1.7 above.]

Changes Made Before Blind Was Broken

The original SAP (09/05/05) stated only that the primary analysis would be performed on the full analysis set. Primary efficacy measure data were also analyzed for the full ITT population, though, in which missing WBF scores were imputed to the worst possible score of 5 (for subjects that were replaced, and for dropouts).

Likewise, key secondary analyses were performed not only on the full analysis set, but also on the ITT population, in which missing pain scores were imputed to the worst possible (VAS score of 100).

The study protocol described a planned analysis of treatment effect size, in which scores (for each subject) from both pain scales (Wong-Baker FACES and VAS) would be combined using “Glass’s meta-analysis.” The final study report states “This analysis was not performed because all subjects were required to complete Wong-Baker FACES, and thus there was no need to combine the two different pain scales into one score.”

The study protocol and SAP described a planned “... secondary efficacy analysis of treatment effect within each age group.” The final study report states that this analysis “...was removed from the SAP via amendment prior to unblinding.” The explanation states, “The power calculation was based on the comparison between active and sham-placebo groups for all age groups combined, so the study would not have been adequately powered to detect the treatment effect within each age group. In addition, the full model for the primary analysis already included treatment-by-age interaction.”

Changes Made After Blind Was Broken

Anesiva did not perform the planned comparison of venipuncture success rate, between treatment groups, “Because the success rate of venipuncture was so similar in the LHM group and the placebo group.”

Unplanned and Post Hoc Analyses

The SAP stated that the primary analysis would be performed on the full analysis set; however, the primary and key secondary analyses were also performed on the ITT population. Missing pain scores were imputed using the worst possible score (Wong- Baker FACES score of 5 and VAS score of 100).

The following “...data-driven post hoc analyses” were also performed:

- A distribution of needle size by treatment group was generated, and treatment effect was examined using an ANOVA model, including treatment group and needle size as independent variables
- A sensitivity analysis was performed, by defining a “responder” as having no pain (Wong-Baker FACES score of 0). The proportions of subjects meeting this criterion were compared between the two treatment groups, using a CMH test stratified by center
- Logistic regression approaches were applied to both of the responder analyses (i.e., the analysis defining responders as having a Wong-Baker FACES score of 0 or 1, and the analysis defining responders as having a Wong-Baker FACES score of 0). The full model included the following independent variables: treatment, age, treatment-by-age interaction, procedure, body site, center, treatment-by-procedure interaction, treatment-by-body site interaction and treatment-by-center
- Proportion of subjects reporting the worst possible pain score was examined (WBF score of 5)

- A comparison of current versus historical pain was conducted using the change in VAS of the parent's assessment of the subject's current pain in this study, compared with the parent's assessment of the subject's historical pain during prior venipuncture or cannulation. This analysis was performed using ANOVA with treatment and age effects in the model
- "In order to confirm the validity of the Wong-Baker FACES assessment, an analysis was performed to assess the correlation of the Wong-Baker FACES results and VAS results in subjects ages 8–18. The Pearson's correlation coefficient and the Spearman's correlation coefficient were estimated."

Changes in Planned Safety Analyses

- The frequency analysis of the investigator or designee's skin assessments was expanded to include descriptive statistics, including N, mean, median, SD, and range.
- Two types of shift analyses were performed for the skin assessment; "one was shift from baseline at post-baseline time point, and the second was shift from the previous time point."
- Hemorrhage/petechiae scores =2 and = 3 were compared by treatment group using a chi-square test.

10.1.9.3 Device Change

The protocol stated that the pressure of the devices to be used would be 20-bar, as in the ND5.3 device. The ND5.3 system had been configured with nominal 20.0-bar microcylinders, at a pressure specification of 20.0-bar \pm 5% (19 – 21-bar). The final, to-be-marketed device, ND5.3A, was utilized in Study 3-003-1, however. The ND5.3A device is configured with nominal 21.0-bar microcylinders, at a pressure specification of 21.0-bar \pm 1.0-bar (20 – 22-bar).

Anesiva contends, that given the overlap in actual pressure ranges, no significant difference would exist, between the ND5.3 and ND5.3A devices. Based upon preliminary assessment, Dr. Pandu Soprey (the CDRH reviewer) agrees, stating in his preliminary review:

The ND5.3A is a final modification of the ND5.3 device with changes in parts design. The changes were made to _____ and the changes were made to the spacer, actuation button, housing boss, nozzle retainers and silencer cover. Performance characteristics of ND5.3A are comparable to ND5.3. Both devices contain 0.5mg sterile LHM powder and the same gas pressure (20-bar). ND5.3A was used in Phase 2 and 3 clinical trials (pivotal trials). The ND5.3A is the final commercial configuration.

b(4)

10.1.10 Applicant Definitions of Protocol Deviations

No categorization scheme for protocol deviations was prospectively defined (i.e., minor vs. major). The study protocol stated:

Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular subject and that are deemed crucial for the safety and well-being of that subject may be instituted for that subject only. The investigator or other attending physician also will contact the medical monitor as soon as possible in the case of such a departure. These departures do not require pre-approval by the IRB; however, the IRB and medical monitor must be notified in writing as soon as possible after the departure has been made. In addition, the investigator will document in the subject's CRF the reasons for the protocol deviation and the ensuing events.

10.1.11 Study Conduct

Protocol 3-003-1 was dated 10/14/04, and conducted between 12/20/04 and 05/06/05. The protocol was amended three times as detailed above in Section 10.1.8. The Statistical Analysis Plan was dated 09/02/05, and revised 09/30/05, both well after enrollment had concluded, but prior to the reported database lock date, 10/05/05. The Clinical Study Report was dated 08/28/06.

Study 3-003-1 was conducted ethically, in accordance with GCP (21CFR §§ 50, 56, and 312), and with the ethical principles of the Declaration of Helsinki. Section 0 above details the measures taken to ensure ethical study conduct and data integrity in Study 3-003-1, as well as the other late-device trials.

For each subject, informed consent was obtained prior to the conduct of any study-related procedures. Consent forms were approved by the appropriate IRBs. Signed informed consent was granted by each subject's parent or legal guardian, and assent to participate was sought according to each site's IRB requirements. Minor documentation issues are described in detail in Section 10.2 of the final study report.

This study was conducted at six US sites, listed in Table 10-3 below. The Principal Investigator was William Zempsky, MD, Connecticut Children's Medical Center, in Hartford, CT.

_____ was the study monitor. _____ functioned as a contract research organization until May 2005. Beginning at that time, Anesiva contracted with individual clinical research associates (CRAs) to monitor the study, and with _____ to provide project management services. _____

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Statistical analysis and data management services were performed by _____

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_____ served as the central study pharmacy. _____ labeled, packaged, stored and distributed the study drug, and unused study drug was to be returned to _____

b(4)

10.1.11.1 Investigators/Study Sites

Six clinical sites were used for Study 3-003-1 as listed in Table 10-3 below. All six were affiliated with academic medical centers. No Contract Research Organizations (CROs) were used. None of the Study 3-003-1 investigators enrolled patients into other Zingo™ trials.

Table 10-3: Study 3-003-1 Investigators and Clinical Sites (Randomized Patients)

| Investigator | Center | Site # | N | PBO | LHM |
|------------------|---------------------------------------|--------|------------|------------|------------|
| J. Bean-Lijewski | Scott & White Memorial Hospital, TX | 01 | 98 | 50 | 48 |
| R. Kauffman | Children's Mercy Hospital, KC, MO | 05 | 99 | 49 | 50 |
| J. Koh | Oregon Health Science University | 06 | 95 | 47 | 48 |
| S. Malviya | University of Michigan | 07 | 52 | 25 | 27 |
| J. Rose | Children's Hospital Philadelphia | 08 | 83 | 41 | 42 |
| W. Zempsky | Connecticut Children's Medical Center | 12 | 152 | 75 | 77 |
| Total | | | 579 | 287 | 292 |

Source: Study 3-003-1 report Appendix 16.1.4 and ISS dataset DEMOG_D

10.1.11.2 Subject Disposition

Five hundred and four pediatric subjects were to complete the study and be evaluable. A total of 579 subjects were enrolled and treated, representing the ITT population (all 549 that were originally randomized and treated, and 30-replacement subjects exposed to treatment). Of these 579, 292 were LHM-treated and 287 were placebo-treated (Table 10-4 below). One additional subject (008-1231) was randomized (to the ages 3-7 group of the LHM group), but never received treatment or had data collected.

This subject was considered a screening failure and was not included in the analysis populations; however, the subject (008-4046) who replaced this screen failure was included in the analysis populations.

Of the 292 subjects treated with LHM, 86 were ages 3–7 years, 94 were ages 8–12 years, and 112 were ages 13–18 years. Of the 287 subjects treated with placebo, 87 were ages 3–7 years, 98 were ages 8–12 years, and 102 were ages 13–18 years. Table 10-4 below summarizes enrollment by treatment and age.

Table 10-4: Study 3-003-1 Subject Enrollment by Treatment Arm, and by Age Group

| | LHM N=292 (%) | Placebo N=287 (%) | Total N=579 (%) |
|---------------------------------|--------------------------------|------------------------------------|----------------------------------|
| Subjects treated ^{1,2} | 292 (100.0) | 287 (100.0) | 579 (100.0) |
| Ages 3–7 years | 86 (29.4) | 87 (30.3) | 173 (29.9) |
| Ages 8–12 years | 94 (32.2) | 98 (34.1) | 192 (33.1) |
| Ages 13–18 years | 112 (38.3) | 102 (35.5) | 214 (37.0) |
| Completed Study | 278 (95.2) | 276 (96.2) | 554 (95.7) |
| Discontinued Study | 14 (4.8) | 11 (3.8) | 25 (4.3) |

¹ Includes initially randomized and replacement subjects

Source: CSR Table 10.3

² One subject (008-1231) was randomized but not treated. No data were collected. This subject is not included in this table or in any sponsor analyses.

Discontinuations

A total of 30 subjects were discontinued from the study: 16 in the LHM group and 14 in the placebo group. One subject in the placebo group (008-1229) was discontinued for administrative reasons (failure to comply with protocol requirements), and the remainder were due to failed first attempt at venipuncture or IV cannulation. Five of these were discontinued in error, the presumed failed initial venipuncture attempts had in fact been successful (LMH-2, Placebo-3).

Thirty replacement subjects (five of these substituted in error) enrolled and received treatment: 17 (5.8%) in the LHM group and 13 (4.5%) in the placebo group:

- Subjects who discontinued were to be replaced. Replacements were assigned for each of the 25 discontinuations, but only 22 of the 25 replacement subjects were enrolled prior to study closing.
- Three subjects were replaced due to protocol violations.
- Five subjects, replaced in error, had WBF scores, thus were included in the full analysis set.

The “full analysis set” includes 574 subjects, 289 LHM-treated and 285 placebo-treated, all with Wong-Baker FACES scores recorded following venipuncture or cannulation. The efficacy evaluable set of 552 subjects, 277 in the LHM group and 275 in the placebo group, included all subjects in the full analysis set except those with failed first attempts at venipuncture, or with “major protocol deviations.” “Major protocol deviations” were not prospectively defined, however.

The efficacy evaluable population consists of 552-subjects (277-LHM, and 275-placebo). A total of 22 subjects included in the full analysis set are excluded from the efficacy evaluable population. These 22 subjects include 19 with failed first venipuncture attempts, two subjects who had “major” protocol violations (prior participation in an LHM study), “...and one subject who was uncooperative and failed to comply with protocol requirements.” (Subject 008-1129, age-5, placebo-group)

Table 10-5 below summarizes enrollment and completion, by age and by applicant-defined analysis set.

Table 10-5: Study 3-003-1 Subject Disposition, by Treatment Group and Age

| | Ages 3-7 | | Ages 8-12 | | Ages 13-18 | | All 3-18 | |
|-----------------------------------|----------|--------|-----------|--------|------------|--------|----------|--------|
| | N | (%) | N | (%) | N | (%) | N | (%) |
| LHM-Treated Population | | | | | | | | |
| ITT Population (exposed) | 86 | (100) | 94 | (100) | 112 | (100) | 292 | (100) |
| Safety Population | 86 | (100) | 94 | (100) | 112 | (100) | 292 | (100) |
| Full analysis set | 86 | (100) | 93 | (98.9) | 110 | (98.2) | 289 | (99.0) |
| Efficacy evaluable set | 84 | (97.7) | 91 | (96.8) | 102 | (91.1) | 277 | (94.9) |
| Completed | 85 | (98.8) | 91 | (96.8) | 102 | (91.1) | 278 | (95.2) |
| Discontinued | 1 | (1.2) | 3 | (3.2) | 10 | (8.9) | 14 | (4.8) |
| Unsuccessful Procedure | 1 | (1.2) | 3 | (3.2) | 10 | (8.9) | 14 | (4.8) |
| Placebo-Treated Population | | | | | | | | |
| ITT Population (exposed) | 87 | (100) | 98 | (100) | 102 | (100) | 287 | (100) |
| Safety Population | 87 | (100) | 98 | (100) | 102 | (100) | 287 | (100) |
| Full analysis set | 85 | (97.7) | 98 | (100) | 102 | (100) | 285 | (99.3) |
| Efficacy evaluable set | 82 | (94.3) | 95 | (96.9) | 98 | (96.1) | 275 | (95.8) |
| Completed | 82 | (94.3) | 95 | (96.9) | 99 | (97.1) | 276 | (96.2) |
| Discontinued | 5 | (5.7) | 3 | (3.1) | 3 | (2.9) | 11 | (3.8) |
| Protocol Deviation* | 1 | (1.1) | 0 | 0 | 0 | 0 | 1 | (0.3) |
| Unsuccessful Procedure | 4 | (4.6) | 3 | (3.1) | 3 | (2.9) | 10 | (3.5) |

Source: 3-003-1 study report Appendix Tables 16.1 and 16.2

*Subject 008-1129 described above

Table 10-6 below summarizes the efficacy analysis sets, by treatment group.

Table 10-6: Study 3-003-1 Analysis Sets, by Treatment Group

| | LHM N=292 (%) | Placebo N=287 (%) | Total N=579 (%) |
|------------------------------------|------------------|----------------------|--------------------|
| Safety/ITT population ¹ | 292 (100.0) | 287 (100.0) | 579 (100.0) |
| Randomized subjects ¹ | 275 (94.2) | 274 (95.4) | 549 (94.8) |
| Replacement subjects ² | 17 (5.8) | 13 (4.5) | 30 (5.2) |
| Full analysis set | 289 (99.0) | 285 (99.3) | 574 (99.1) |
| Efficacy evaluable set | 277 (94.9) | 275 (95.8) | 552 (95.3) |

¹Subject 008-1231 was randomized but not treated; no efficacy data were collected.

This subject was not included in this table, or in any of the statistical analyses.

²Subjects with failed first venipuncture attempts were replaced, as were all other discontinuations.

Source: CSR Section-14, Table-1 and Appendix 16, Listing 1.2

10.1.11.3 Protocol Deviations and Violations

Protocol deviations are detailed in data listing 16.2.2.1.4, and summarized in Table 10-7 below. The most common involved minor deviations from the safety assessment schedule, and investigator incorrect categorization of failed first procedure attempts (as deviations). Five subjects were replaced in error;

investigators failed to recognize the success of the initial procedure attempt. The most noteworthy protocol deviations were:

- Two enrolled subjects had previously been in LHM trials. This was discovered prior to database lock for one subject (012-1027), who was replaced. Another subject, who was discovered subsequent to database lock (012-3111), had completed the study. Both were labeled “major protocol violations” and excluded from the efficacy evaluable population.
- Subject 008-3231 had grade-1 erythema at the site of administration throughout the study period (before and after study treatment), and thus did not meet the eligibility criteria. This subject completed the study, was not replaced and was included in all analysis sets.
- Subject 008-1229 was uncooperative and failed to comply with protocol requirements. This subject completed the study, was replaced and was excluded from the efficacy evaluable set.
- Five subjects (001-2090, 007-2161, 007-3163, 007-3165 and 007-3167) were replaced in error. These subjects were replaced due to perceived failed first attempts at venipuncture or cannulation. In each case the procedure was later deemed to have been successful, and is classified accordingly in the database. Both the original and replacement subjects are included in all analysis sets.

Table 10-7: Study 3-003-1 Protocol Deviations

| Deviation Category | LHM | | PBO | | ALL | |
|--------------------------|-----------|----------------|------------|----------------|------------|----------------|
| | N=292 (%) | | N=287 (%) | | N=579 (%) | |
| Informed Consent/Assent | 2 | (0.7%) | 5 | (1.7%) | 7 | (1.2%) |
| Study Entry Criteria | 2 | (0.7%) | 1 | (0.3%) | 3 | (0.5%) |
| Visit Schedule | 17 | (5.8%) | 22 | (7.7%) | 39 | (6.7%) |
| Procedures/Tests | 41 | (14.0%) | 44 | (15.3%) | 85 | (14.7%) |
| Randomization | 1 | (0.3%) | 4 | (1.4%) | 5 | (0.9%) |
| Other | 6 | (2.1%) | 4 | (1.4%) | 10 | (1.7%) |
| Non Relevant Deviations* | 29 | (9.9%) | 42 | (14.6%) | 71 | (12.3%) |
| TOTAL | 88 | (30.1%) | 102 | (35.5%) | 190 | (32.8%) |

Source: Applicant response 3/15/2007 and ISS dataset DEMOG.XPT * Failed first procedure, miscategorized

Consent/ Assent Issues

- Although assent for all subjects was specified as a requirement in the study protocol, it was not consistently sought and recorded. Some participating IRBs required children’s assent only for specific age ranges, or not at all. Investigators generally followed policies of their institution and IRB.
- Subject 012-1005 was found to have an unsigned (by parent) informed consent. This deviation was not noted until days later. The monitoring site documentation indicates that the parent was present and approved of the subject being in the study. This subject’s data were included in all analyses.
- Fourteen other minor consent/assent issues are described in the data listings (16.2.2.1.4). One consent form was not signed by the investigator, and another one was dated incorrectly by the child. The other twelve were assent forms that were not collected due to site error or lack of IRB requirements.
- Additional minor deviations included incomplete investigator skin assessments, telephone contact information, “... and pain assessments that were incomplete or performed outside of the protocol-specified schedule.”

These protocol deviations occurred in similar proportions in the two treatment groups. Overall, they are unlikely to have impacted study results in any appreciable way. My conclusions regarding the 3-003-1 results would not differ in their absence.

10.1.12 Demographics/Group Comparability

10.1.12.1 Subject Demographics

Subject baseline demographic characteristics are summarized in Table 10-8 below. Review of these data shows that demographic characteristics were comparable across treatment conditions, though not necessarily representative of the general US population. Subject demographics were similarly comparable across age groups (as evidenced by CSR Tables 14.1.2.2, 14.1.2.3 and 14.1.2.4).

Table 10-8: Study 3-003-1 Subject Demographics (ITT Population)

| Characteristic | LHM N=292 (%) | Placebo N=287 (%) | All N=579 (%) |
|--------------------|------------------|----------------------|------------------|
| Gender | | | |
| Male (%) | 139 (47.6) | 137 (47.7) | 276 (47.7) |
| Female (%) | 153 (52.4) | 150 (52.3) | 303 (52.3) |
| Age (years) | | | |
| Mean ± SD | 10.6 ± 4.3 | 10.5 ± 4.2 | 10.5 ± 4.2 |
| Median | 11.0 | 11.0 | 11.0 |
| Range | 3 - 18 | 3 - 18 | 3 - 18 |
| [3 - 7] | 86 | 87 | 173 |
| [8 - 12] | 94 | 98 | 192 |
| [13 - 18] | 112 | 102 | 214 |
| Ethnicity | | | |
| Caucasian | 253 (86.6) | 230 (80.1) | 483 (83.4) |
| Black | 23 (7.9) | 35 (12.2) | 58 (10.0) |
| Asian | 2 (0.7) | 5 (1.7) | 7 (1.2) |
| Pacific Islander | 1 (0.3) | 2 (0.7) | 3 (0.5) |
| Other | 13 (4.5) | 15 (5.2) | 28 (4.8) |
| Weight (kg) | | | |
| Mean ± SD | 43.6 ± 21.3 | 42.3 ± 20.9 | 43.0 ± 21.1 |
| Median | 40.5 | 38.8 | 40.0 |
| Range | 11.8 - 113.7 | 13.0 - 124.7 | 11.8 - 124.7 |

Source: Study 3-003-1 report Tables 11.2.5 and 14.1.2.1 (CSR Section-14)

10.1.12.2 Baseline Medical Conditions (Medical History)

Subjects' previous medical history is not described within the text of the study report. In general, subjects were healthy, without chronic disease or significant comorbidities. The most frequent reasons for venipuncture/IV, summarized were roughly equally distributed between treatment groups.

Vital signs were not obtained at screening, nor was laboratory testing done.

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10.1.13 Study 3-003-1 Efficacy Results

10.1.13.1 Primary Efficacy Data

The primary efficacy measure was subjects' assessment of pain, from venipuncture or peripheral venous cannulation performed one to three minutes after drug administration, measured using the Wong-Baker FACES scale, anchored at 0 for "no hurt" and 5 for "hurts worst" for all ages (3–18 years).

Though not specified as the primary analysis, WBF data were compared between treatment groups for the entire ITT population, which included all treated subjects, regardless of whether or not venipuncture was performed, or WBF pain score obtained. Missing scores were imputed to the worst value, "5."

The results of the ITT analysis are summarized in Table 10-9 below. Treatment with LHM resulted in statistically significantly ($p = 0.011$) less pain, from venipuncture or IV cannulation, compared with placebo. The difference in LSMs was rather small, however (-0.33 ± 0.13).

Table 10-9: Study 3-003-1 Wong-Baker FACES Score (ITT)

| | LHM (N=292) | Placebo (N=287) |
|-------------------------|------------------------|----------------------------|
| Adjusted Mean, LSM | 1.77 | 2.10 |
| Standard Error of LSM | 0.09 | 0.09 |
| Difference in LSMs (SE) | -0.33 (0.13) | |
| p-value | 0.011 | |
| 95% Confidence Limits | -0.58, -0.08 | |

Source: Study 3-003-1 report Tables 11.1.10 and 5.1.1B

The applicant specified as primary, analysis of WBF data for the full analysis population (FAP), all treated subjects (who underwent venipuncture or IV cannulation) with primary efficacy endpoint (WBF score). This population included all originally randomized and replacement subjects. Missing WBF scores, such as those for subjects replaced after unsuccessful venipuncture attempt, were NOT imputed. Data from these subjects were not included in this analysis.

The results of the applicant's primary analysis are summarized in Table 10-10 below. These findings are consistent with those for the ITT population, though of slightly greater magnitude.

Table 10-10: Study 3-003-1 Wong-Baker FACES Score (FAS)

| | LHM (N=289) | Placebo (N=285) |
|-------------------------|------------------------|----------------------------|
| Adjusted Mean, LSM | 1.73 | 2.08 |
| Standard Error of LSM | 0.09 | 0.09 |
| Difference in LSMs (SE) | -0.34 (0.13) | |
| p-value | 0.007 | |
| 95% Confidence Limits | -0.60, -0.09 | |

Source: Study 3-003-1 report Tables 11.1.9 and 5.1.1

10.1.13.2 Key Secondary Efficacy Data

The key secondary efficacy findings support those for the primary analysis.

Subject Assessment of Pain Using 100-mm VAS (Ages 8 – 18)

Subjects ages eight through eighteen reported (statistically significantly) less procedure-related pain, as measured by 100-mm VAS, when pre-treated with LHM, compared with placebo (Table 10-11).

Table 10-11: Study 3-004-1, Subject VAS, Ages 8-18

| | <u>ITT Population</u> | | <u>FAS Population</u> | |
|-------------------------|-----------------------|---------------------------|-----------------------|---------------------------|
| | <u>LHM</u> (N=206) | <u>Placebo</u> (N=200) | <u>LHM</u> (N=203) | <u>Placebo</u> (N=200) |
| Adjusted Mean, LSM | 22.62 | 31.97 | 21.50 | 31.97 |
| Standard Error of LSM | 1.80 | 1.82 | 1.76 | 1.77 |
| Difference in LSMs (SE) | -9.35 (2.56) | | -10.5 (2.49) | |
| p-value | <0.001 | | <0.001 | |
| 95% Confidence Limits | -14.4, -4.31 | | -15.4, -5.56 | |

Source: Study 3-003-1 report Table 11.1.11 and Appendix Table 5.2.1.B

Parent Assessment of Child's Pain, Using 100-mm VAS (Ages 3 – 18)

Parents perceived their children to experience less procedure-related pain, as assessed by 100-mm VAS, when pre-treated with LHM, compared with placebo (Table 10-12 below). The ITT and FAS populations were identical, because parent VAS data were missing for the same 12-subjects in each population.

**Table 10-12: Study 3-003-1 Parent Assessment of Child's Pain
100-mm VAS, Ages 3-18 (ITT Population and also FAS Population)**

| | <u>LHM</u> (N = 292) | <u>Placebo</u> (N = 287) |
|-------------------------|-------------------------|-----------------------------|
| Available data | N=285 | N=282 |
| Adjusted Mean, LSM | 21.69 | 28.92 |
| Standard Error of LSM | 1.54 | 1.54 |
| Difference in LSMs (SE) | -7.24 (2.18) | |
| p-value | ≈0.001 | |
| 95% Confidence Limits | -11.5, -2.96 | |

Source: Study 3-003-1 report Table 5.4.1B, Section-14

10.1.13.3 Treatment Effect by Study Center

Anesiva's analysis of treatment effect by treatment center, compared differences in VAS-scores (between treatment groups), in 8-18 year-olds (younger children did not complete the VAS), in the FAS population only. Centers 01, 07 and 06 appear to be driving the overall VAS efficacy results.

My own analysis was conducted on the primary efficacy measure, the FACES score, for the complete ITT population (the overall primary efficacy analysis). These data show that Center 12 and 01 are largely driving the primary efficacy findings. Center 12, the Primary Investigator's center, enrolled considerably more subjects than any other clinical site. Center 01 was also one of the higher enrollers, contributing

17% of subjects. For these reasons, these two clinical centers were chosen for routine DSI inspection (along with two Study 3-004-1 centers).

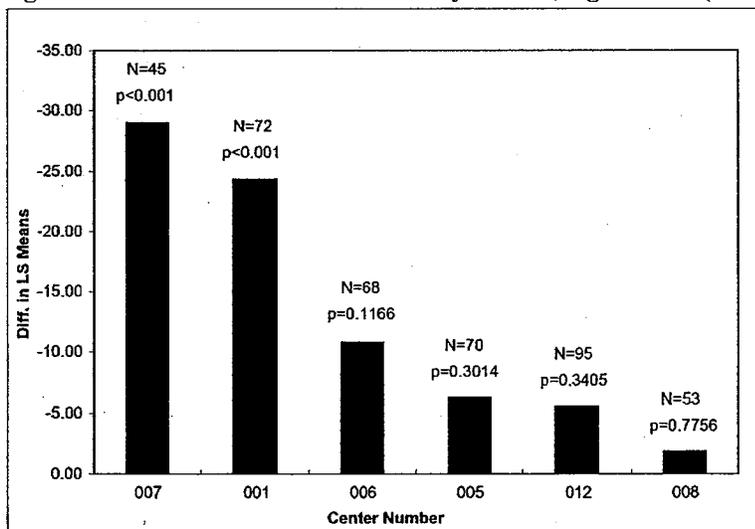
Table 10-13: Study 3-003-1 Treatment Effect by Treatment Center

| | ^a VAS-Ages 8-18 (FAS Only) | | | | ^b FACES-All Ages (ITT) | |
|------------|---------------------------------------|--------------|---------|-----|-----------------------------------|-----|
| | VAS Difference | | | | FACES | |
| | LS-Means Δ (SE) | 95%-CI | P-Value | N | P-Value | N |
| Center #01 | -24.3 (6.73) | -37.5, -11.0 | <0.001 | 72 | 0.061 | 98 |
| Center #05 | -6.32 (6.10) | -18.3, 5.69 | =0.301 | 70 | 0.953 | 99 |
| Center #06 | -10.9 (6.91) | -24.4, 2.72 | =0.117 | 68 | 0.923 | 95 |
| Center #07 | -29.0 (8.16) | -45.0, -12.9 | <0.001 | 45 | 0.095 | 52 |
| Center #08 | -1.89 (6.64) | -14.9, 11.16 | =0.776 | 53 | 0.548 | 83 |
| Center #12 | -5.59 (5.86) | -17.1, 5.92 | =0.341 | 95 | 0.043 | 152 |
| Overall | -10.5 (2.49) | -15.4, -5.56 | <0.001 | 403 | 0.011 | 579 |

Sources: ^aStudy 3-003-1 report Table 14.5.2.1

^bClinical reviewer- One-way ANOVA

Figure 10-3: VAS Difference in LSM by Center, Ages 8 - 18 (FAS)



Source: Study 3-003-1 Diagram 15.5.1

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10.1.14 Procedure Performed

Venipuncture was performed in 42.0% of subjects, and peripheral vein cannulation was performed in 58.0%. The ACF was the treatment site in 54.7% of subjects, and the BOH was chosen in 45.3%. No differences were apparent between the LHM placebo treatment groups, with respect to procedures performed or anatomic site. These data are summarized in Table 10-14 below.

Table 10-14: Study 3-003-1 Procedure Performed and Treatment Site (ITT)

| | Number (%) of Subjects | | |
|----------------------------|------------------------|----------------------|--------------------|
| | LHM (N = 292) | Placebo (N = 287) | Total (N = 579) |
| Procedure Performed | | | |
| Cannulation | 167 (57.2) | 169 (58.9) | 336 (58.0) |
| Venipuncture | 125 (42.8) | 118 (41.1) | 243 (42.0) |
| Body Site | | | |
| Antecubital fossa (ACF) | 158 (54.1) | 159 (55.4) | 317 (54.7) |
| Back of hand (BOH) | 134 (45.9) | 128 (44.6) | 262 (45.3) |

Source: Study 3-003-1 report, Table 11.2.2.3

Subjects in both treatment groups underwent venipuncture or cannulation with needle sizes ranging from 18– 25 gauge. The distribution of needle sizes was similar in the two treatment arms

10.1.15 Discussion of Study 3-003-1 Efficacy Findings

Although the absolute magnitude of the treatment effect was fairly small, the Study 3-003-1 data appear to provide support for Anesiva’s primary efficacy claim; Zingo™ provides local analgesia when administered on intact skin one to three minutes prior to venipuncture or peripheral intravenous cannulation.

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10.2 Study 3-004-1

A Phase III, Randomized, Double-Blind, Placebo-Controlled Study to Confirm the Effectiveness and Safety of ALGRX 3268 in Pediatric Subjects

[Note: Identical to Study 3-003-1 (Section 10.1) in design, population, efficacy measures and analyses]

10.2.1 Findings vs. Labeling Claims

The Study 3-004-1 efficacy findings support the Applicant's efficacy claim for the proposed indication. Subjects treated with Zingo™ one to three minutes prior to venipuncture or intravenous cannulation, reported less procedure-related pain than those treated with placebo.

10.2.2 Study Plan

The initial version of Protocol 3-003-1 was dated 11/18/2004. Two amendments were implemented, both prior to initiation of study enrollment (See Section 10.2.9 below). The Statistical Analysis Plan was dated 08/21/2005 and revised 09/30/2005. (Database lock was 10/31/2005.)

10.2.3 Objectives, Design and Population

10.2.3.1 Objectives

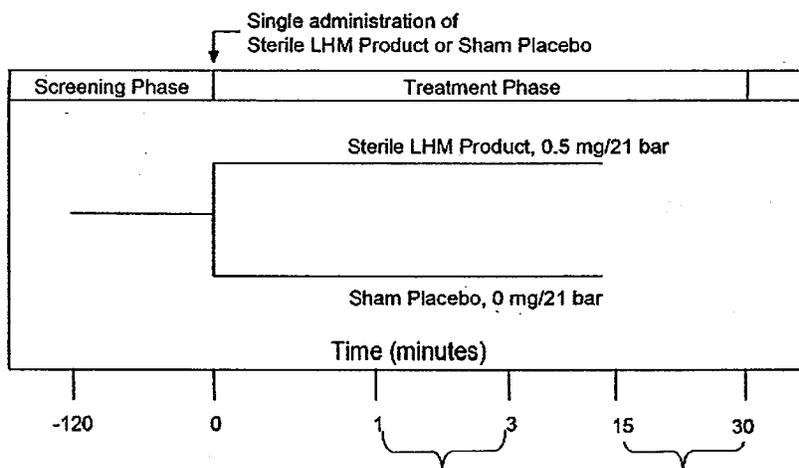
The protocol-specified primary objective of Study 3-003-1 was "To confirm the efficacy of ALGRX3268 compared to placebo in pediatric subjects."

The protocol-specified secondary objective was "To confirm the safety and tolerability of ALGRX3268 compared to placebo in pediatric subjects."

10.2.3.2 Design

Study 3-004-1 was designed as a multi-center, randomized, DB-PC, parallel-group, single-dose study, in pediatric subjects undergoing (medically necessary) venipuncture or peripheral venous cannulation at the antecubital fossa or back of hand. Figure 10-1 above diagrams the study design.

Figure 10-4: Study 3-004-1 Design – Treatment and Assessment Schedule



Minute (-120)

- Informed consent, Demographics, Reason for procedure, Inclusion/Exclusion criteria, Concomitant medications, Parent assessment of child's perception of anticipated pain of procedure
- Randomization if eligible

Minute (Zero)

- Study drug administration
- Dermal assessment of drug administration site (immediately before and after dosing)
- AEs, Concomitant medication

Minute (+1)

- Venipuncture or peripheral venous cannulation (pain model)

Minutes (+1) to (+3)

- Child scores pain (Wong-Baker FACES for all + 100-mm VAS for ages 8 – 18))
- Parent scores child's pain (100-mm VAS)
- Investigator categorizes procedure (venipuncture/IV) as success or procedure
- AEs, Concomitant medications
- Dermal assessment of drug administration site

Minutes (+15) to (+30)

- Dermal assessment of drug administration site
- AEs, Concomitant medications

10.2.3.3 Population

Five hundred and four (N=504) pediatric subjects, ages three through eighteen, scheduled to undergo venipuncture or peripheral venous cannulation, were to be enrolled.

Inclusion criteria were to be:

1. Children of either gender who are to undergo venipuncture or peripheral venous cannulation at the antecubital fossa or the back of the hand.
2. Ages 3 to 18 inclusive; grouped as 3 to 7 years, 8 to 12 years, and 13 to 18 years.
3. Children must have sufficient cognitive skills to identify faces depicting extremes of pain on the Wong-Baker FACES pain rating scale (the FACES scale; ages 3-18) and the extremes of pain on a 100 mm visual analog scale (VAS; ages 8-18).
4. Consent forms must be approved by the appropriate IRBs. Signed informed consent must be granted by the parent/legal guardian and assent to participate should be sought (either verbally or in writing) from each child.
5. In females who have reached menses, and who – in the judgment of the investigator or designee are sexually active – a negative urine pregnancy test must be documented prior to enrollment. A negative urine pregnancy test is required in all teenage girls who have reached menses or are over 14 years old.

Exclusion Criteria were to be:

1. Previous history of allergic reaction to any local anesthetic or tape/adhesive dressing.
2. Any medical condition or instability that in the judgment of the investigator might adversely impact the conduct of the study and the collection of data.
3. Active local infection or skin pathology at the site of venipuncture or peripheral venous cannulation.
4. Subjects with tattoos, surgical scars, ports, implantable devices or a skin condition that may interfere with product placement or skin site assessments.
5. Female subjects who are pregnant or lactating; females with a positive serum or urine pregnancy test; females of childbearing potential who are not using adequate contraception.
6. Prior participation in an ALGRX 3268 study.

7. Venipuncture or peripheral venous catheter insertion at the proposed site within the prior two weeks (longer if bruising is apparent).
8. Any child deemed uncooperative or exceptionally upset prior to study drug administration.
9. The subject has taken any investigational medication within 1 month prior to administration of study drug or is scheduled to receive an investigational drug other than ALGRX 3268 while participating in the study.

Minor deviations from entry criteria were to be "... allowed only if the investigator and the medical monitor agree in writing prior to subject enrollment.

10.2.4 Study Treatment

Randomization/Informed Consent

Each investigational center was to receive its own computer-generated randomization schedule. Distribution of subjects to active or placebo was to be in a 1:1 ratio. Every subject who signed (or whose guardian signed) the informed consent, was to be assigned a subject number, unique to Study 3-003-1. Drug administration site would be investigator-assigned, depending on clinical conditions.

Randomization was to be stratified, by study center and by age group (3 to 7 years, 8 to 12 years and 13 to 18 years). Enrollment for an age group was to be discontinued when the target number had been attained. Subjects were to be approximately equally distributed across gender, within each age group.

Study Drug Treatment

Patients were to receive one of two treatments, one to three minutes prior to venipuncture or intravenous cannulation;

- Lidocaine 0.5-mg intradermally at 21-bar (volume of solution?)
- Placebo intradermally at 21-bar (volume of solution?)

Prohibited Concomitant Medication/Therapy

"Other local anesthetic products" were not to be administered at the site of venipuncture or peripheral venous cannulation, from screening until after study completion or withdrawal. All other concomitant medications were to be recorded in the CRF.

Replacement of Subjects

Discontinuations prior to completion of the primary efficacy assessment were to be replaced. The replacement subject was to receive the same treatment as the discontinued subject. Dropouts that had received study treatment were to be included in the primary ITT analysis, and in the safety analyses. A replacement subject was to be enrolled for each discontinuation (to the same treatment arm). Subjects were to be discontinued by the investigator (and replaced) for;

- Failed initial venipuncture/IV attempts
If venipuncture or cannulation was not successful on the first attempt, subjects were to be considered "... non-evaluable due to the confounding effects of multiple needle insertions." Subjects whose venous procedure was not successful on the first attempt were to be discontinued from the study, and replaced with another subject. Replacement subjects were each to be assigned to the same treatment arm as the originally randomized subject they would be replacing.
- Instances of device failure

Replacement subjects were also to be assigned for each subject for which the drug delivery device failed to actuate (same treatment condition). A central facility would be responsible for assigning replacement numbers.

10.2.5 Screening Assessment

Assessments performed at screening were to include:

- Review of inclusion and exclusion criteria and elicitation of demographic data
- Documentation of the reason for the venipuncture/IV.
- Negative pregnancy tests were to be required for some, but not all female subjects. The protocol included the following instructions to investigators;
In females who have reached menses, and who – in the judgment of the investigator or designee are sexually active – a negative urine pregnancy test must be documented prior to enrollment. A negative urine pregnancy test is required in all teenage girls who have reached menses or are over 14 years old.
- Children in the 3 to 7 year age group were to be given a “seriation test,” in which they would be asked to place six triangles in size order, from smallest to largest. Children able to complete the task would be considered capable of identifying the extremes of pain depicted on the Wong-Baker FACES.

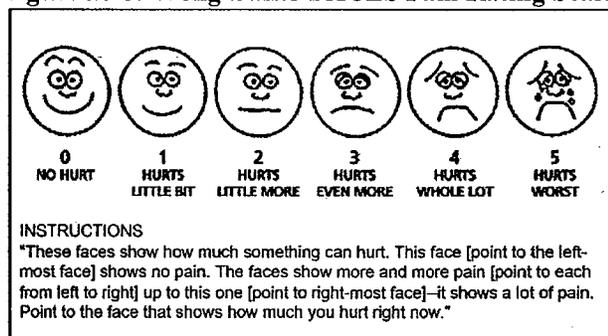
10.2.6 Efficacy Assessment

Table 10-15 below and Figure 10-4 above summarize the overall schedule for Study 3-004-1 efficacy assessment and procedures.

10.2.6.1 Primary Efficacy Measure

The primary efficacy measure, in all age groups, was to be the subject’s assessment of pain, from venipuncture or intravenous cannulation one to three minutes after study drug administration. The pain assessment instrument was to be the Wong-Baker-FACES pain rating scale, a six-point scale anchored at zero (“No Hurt”) and five (“Hurts Worst”), as shown in Figure 10-5 below.

Figure 10-5: Wong-Baker FACES Pain Rating Scale



The instructions to subjects were modified from those in the original description of the Wong-Baker FACES instrument, as described in Section 10.1.6.1 above. The instructions utilized throughout product development were based on the Faces Pain Scale-Revised, as described and validated by Hicks.

10.2.6.2 Secondary Efficacy Measures

Key secondary efficacy measures were to be subjects' assessment of pain using;

- 100-mm VAS score (0 (zero) for "No Pain" to 100 for "Extreme Pain"), for children in the middle (ages 8-12) and oldest (ages 13-18) age groups combined.
- The Wong-Baker FACES pain rating scale, analyzed separately by age group (ages 3-7, 8-12, 13-18)

Additional secondary efficacy measures were to include;

- Treatment effect size, by combining the two different pain scales using Glass's meta-analysis
- Parents' assessment of child's pain, following venipuncture/IV, measured using 100-mm VAS
- Success rate of venipuncture or peripheral venous cannulation.

Table 10-15: Study 3-004-1 Assessment and Event Schedule

| Assessment / Event | Screening (-120) Mins. | Treatment 0 Mins. | Treatment 1-3 Mins. | Treatment 15 Mins. | Treatment 30 Mins. |
|---|------------------------|-------------------|---------------------|--------------------|--------------------|
| Consent / Demographics | X | | | | |
| Reason for Venipuncture/IV | X | | | | |
| Urine Pregnancy in Females ^a | X | X | | | |
| Inclusion/Exclusion Criteria | X | X | | | |
| Study Drug Administration | | X | | | |
| Venipuncture/ IV Cannulation | | | | X | |
| Efficacy Assessments | | | | X | |
| Vital Signs | | X | | | X |
| Skin Assessment, AEs | | X ^b | X | X | X |
| Concomitant Medications | X | X | X | | X |

^a "In females who have reached menses, and who – in the judgment of the investigator or designee are sexually active – a negative urine pregnancy test must be documented prior to enrollment. A negative urine pregnancy test is required in all teenage girls who have reached menses or are over 14 years old. Where the Treatment Phase immediately follows the Screening Phase on the same day, only one pregnancy test is required."

^b ACF or BOH assessed for erythema, edema, pruritus, hemorrhage or petechiae, just before and after study drug admin.

10.2.7 Statistical Analysis Plan

The Statistical Analysis Plan was dated August 21, 2005, and revised September 30, 2005. Both dates were well after enrollment had concluded, but prior to the reported database lock date, October 31, 2005.

Sample Size Calculation

The target sample size was based upon data from the earlier Study 2-002-1, in which ALGRX 3268 was administered to children ages 3-18, at the BOH. Anesiva states that the 2-002-1 results indicated that the mean WBF scores for children ages 3-12 were 1.25 and 1.91, for the active and the placebo groups, respectively. The standard deviation was 1.65. In order to detect the same pain score difference between treatment conditions, with 90% power, using a 5% significance level (two-sided), 135-subjects per treatment group would be required.

The statistical analysis plan went on, however, to state "Therefore, 252 subjects for each treatment group will have more than 90% power for detecting a desired pain score difference. In order to insure a balanced number of 3 age groups of children, a sample size of 168 children within each age group will be

randomized to either ALGRX 3268 or placebo treatment group. Therefore, a total of 504 children will be recruited in this study. In addition, this sample size will allow enough subjects to be assessed for the safety parameters. “

Analysis Populations

Efficacy analyses were to be performed on three analysis populations;

- The full analysis set, including subjects who received study treatment and had recorded results for the primary efficacy endpoint (Wong-Baker FACES) following venipuncture or IV cannulation.
 - This set was to include both originally randomized subjects and replacement subjects.
- The safety population (which is also intent-to-treat (ITT) population), including all subjects who received study drug.
- The efficacy evaluable set (per protocol), including all subjects in the full analysis set, except for subjects with major protocol violations, as determined by Anesiva prior to breaking the blind.

Analyses

Continuous variables would be summarized by the mean, median, standard deviation (SD), range and N. Categorical variables would be summarized by the frequency and percentage of subjects in each category.

A two-sided test with a significance level of 0.05 was to be used for any hypothesis testing (except for interaction testing, for which 0.10 was to be used). In addition, the 95% confidence interval was to be provided for the point estimate.

Each subject was to be categorized into one of three age groups. Summary tables were to be presented separately for each of the three age groups. All summary tables were also to be presented for all subjects combined “... to identify the treatment effect across age groups.” If a subject were randomized to an incorrect age group, their data were to be summarized and analyzed based upon the correct age group.

10.2.8 Safety Data

AEs were to be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 5.1. Concomitant medications were to be categorized using the World Health Organization Drug Reference List (WHO-Drug, no version specified).

10.2.9 Changes in Study Conduct or Planned Analyses

10.2.9.1 Protocol Amendments

There were two amendments to Protocol 3-004-1. Both were implemented prior to study initiation.

The first, dated December 02, 2004 made minor revisions to the study medication label, identical to those made for Study 3-003-1, detailed in Table 10-2 on page-77.

The second amendment (January 18, 2005) removed references to the “coordinating investigator” because Study 3-004-1 did not have an overall coordinating investigator. Minor editorial changes were also made.

The remaining items from the second amendment were “...implemented on a per-site basis, based on local IRB policy.”

- An inclusion criterion, requiring a negative urine pregnancy test prior to enrollment was deleted.

- The following exclusion criterion was deleted: "Female subjects who are pregnant or lactating; females with a positive serum or urine pregnancy test; females of childbearing potential who are not using adequate contraception."

10.2.9.2 Changes in the Planned Analyses

[The SAP and subsequent revision were identical to those for Study 3-003-1, except for the dates.]

The original SAP (dated 09.05/05), was revised September 30, 2005, after enrollment had concluded, but prior to the reported database lock date, October 31, 2005.

The original SAP stated only that the primary analysis would be performed on the full analysis set. Primary efficacy measure data were also analyzed for the full ITT population, though, in which missing WBF scores were imputed to the worst possible score of 5 (for subjects that were replaced, and for dropouts).

Likewise, key secondary analyses were performed not only the full analysis set, but also on the ITT population, in which missing pain scores were imputed to the worst possible (VAS score of 100).

The study protocol described a planned analysis of treatment effect size, in which scores (for each subject) from both pain scales (Wong-Baker FACES and VAS) would be combined using "Glass's meta-analysis." The final study report states "This analysis was not performed because all subjects were required to complete Wong-Baker FACES, and thus there was no need to combine the two different pain scales into one score."

The study protocol and SAP described a planned "... secondary efficacy analysis of treatment effect within each age group." The final study report states that this analysis "...was removed from the SAP via amendment prior to unblinding." The explanation states "The power calculation was based on the comparison between active and sham-placebo groups for all age groups combined, so the study would not have been adequately powered to detect the treatment effect within each age group. In addition, the full model for the primary analysis already included treatment-by-age interaction."

Anesiva did not perform the planned comparison of venipuncture success rate, between treatment groups, "Because the success rate of venipuncture was so similar in the LHM group and the placebo group."

Post Hoc Analyses

The SAP stated that the primary analysis would be performed on the full analysis set; however, the primary and key secondary analyses were also performed on the ITT population. Missing pain scores were imputed using the worst possible score (Wong- Baker FACES score of 5 and VAS score of 100).

The following "...data-driven post hoc analyses" were also performed;

- A distribution of needle size by treatment group was generated, and treatment effect was examined using an ANOVA model, including treatment group and needle size as independent variables
- A sensitivity analysis was performed, by defining a "responder" as having no pain (Wong-Baker FACES score of 0). The proportions of subjects meeting this criterion were compared between the two treatment groups, using a CMH test stratified by center

- Logistic regression approaches were applied to both of the responder analyses (i.e., the analysis defining responders as having a Wong-Baker FACES score of 0 or 1, and the analysis defining responders as having a Wong-Baker FACES score of 0). The full model included the following independent variables: treatment, age, treatment-by-age interaction, procedure, body site, study center, treatment-by-procedure interaction, treatment-by-body site interaction and treatment-by-center
- Proportion of subjects reporting the worst possible pain score was examined (Wong-Baker FACES score of 5)
- A comparison of current versus historical pain was conducted using the change in VAS of the parent's assessment of the subject's current pain in this study, compared with the parent's assessment of the subject's historical pain during prior venipuncture or cannulation. This analysis was performed using ANOVA with treatment and age effects in the model
- "In order to confirm the validity of the Wong-Baker FACES assessment, an analysis was performed to assess the correlation of the Wong-Baker FACES results and VAS results in subjects ages 8-18. The Pearson's correlation coefficient and the Spearman's correlation coefficient were estimated."

Changes in Planned Safety Analyses

- The frequency analysis of the investigator or designee's skin assessments was expanded to include descriptive statistics, including N, mean, median, SD, and range.
- Shift analyses for the skin assessment were performed. Two kinds of shift analysis were performed: one was shift from baseline at post-baseline time point, and the second was shift from the previous time point.
- Hemorrhage/petechiae scores =2 and = 3 were compared by treatment group using a chi-square test.

10.2.9.3 Device Changes

The protocol stated that the pressure of the devices to be used would be 20-bar, as in the ND5.3 device. The ND5.3 system had been configured with nominal 20.0-bar microcylinders, at a pressure specification of 20.0-bar \pm 5% (19 – 21-bar). The final, to-be-marketed device, ND5.3A, was utilized in Study 3-003-1, however. The ND5.3A device is configured with nominal 21.0-bar microcylinders, at a pressure specification of 21.0-bar \pm 1.0-bar (20 – 22-bar).

Anesiva contends, that given the overlap in actual pressure ranges, no significant difference would exist, between the ND5.3 and ND5.3A devices. Based upon preliminary assessment, Dr. Pandu Soprey (the CDRH reviewer) agrees, stating in his preliminary review:

The ND5.3A is a final modification of the ND5.3 device with changes in parts design. The changes were made to τ and the changes were made to the spacer, actuation button, housing boss, nozzle retainers and silencer cover. Performance characteristics of ND5.3A are comparable to ND5.3. Both devices contain 0.5mg sterile LHM powder and the same gas pressure (20-bar). ND5.3A was used in Phase 2 and 3 clinical trials (pivotal trials). The ND5.3A is the final commercial configuration.

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10.2.10 Applicant Definitions of Protocol Deviations

No categorization scheme for protocol deviations was prospectively defined (i.e., minor vs. major). The study protocol stated;

Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular subject and that are deemed crucial for the safety and well-being of that subject may be instituted for that subject only. The investigator or other attending physician also will contact the medical monitor as soon as possible in the case of such a departure. These departures do not require pre-approval by the IRB; however, the IRB and medical monitor must be notified in writing as soon as possible after the departure has been made. In addition, the investigator will document in the subject's CRF the reasons for the protocol deviation and the ensuing events.

10.2.11 Study Conduct

Protocol 3-004-1 was dated 11/18/04, and conducted between 02/03/05 and 07/14/05. The protocol was amended twice prior to enrollment, as detailed in Section 10.1.9.1 above. The Statistical Analysis Plan was dated 09/02/05, and revised 09/30/05, both well after enrollment had concluded, but prior to the reported database lock date, 10/05/05. The Clinical Study Report was dated 08/28/06.

Study 3-004-1 was conducted ethically, in accordance with GCP (21CFR §§ 50, 56, and 312), and with the ethical principles of the Declaration of Helsinki. Section 0 above details the measures taken to ensure ethical study conduct and data integrity in Study 3-004-1, as well as the other Phase-2/3 trials.

For each subject, informed consent was obtained prior to the conduct of any study-related procedures. Consent forms were approved by the appropriate IRBs. Signed informed consent was granted by each subject's parent or legal guardian, and assent to participate was sought according to each center's IRB requirements. Minor documentation issues are described in detail in Section 10.2 of the final study report.

This study was performed at nine US study centers, listed in Table 10-16 below.

_____ was the study monitor _____ functioned as a contract research organization until May 2005. Beginning at that time, Anesiva contracted with individual clinical research associates (CRAs) to monitor the study, and with _____ to provide project management services _____

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Statistical analysis and data management services were performed by _____

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_____ served as the central study pharmacy. _____ labeled, packaged, stored and distributed the study drug, and unused study drug was to be returned to _____

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10.2.11.1 Investigators/Study Centers

Nine clinical centers were used for Study 3-004-1, listed in Table 10-16 below. Six were affiliated with academic medical centers, while three were CROs. No study coordinator or Principal Investigator was designated. None of the Study 3-004-1 investigators enrolled patients into other Zingo™ trials.

Table 10-16: Study 3-004-1 Investigators and Clinical Centers (ITT Population)

| Investigator | Center | Site # | N | PBO | LHM |
|---------------------------|--|--------|------------|------------|------------|
| | | 02 | 2 | 0 | 2 |
| J. Finkel | Children’s National Medical Center, DC | 03 | 106 | 51 | 55 |
| E. Krane and G. Hammer | Stanford University Medical Center Department of Anesthesia | 04 | 73 | 36 | 37 |
| M. Rossberg | Johns Hopkins Hospital, Anesthesia | 09 | 27 | 15 | 12 |
| M. Schmitz | Arkansas Children’s Hospital | 10 | 100 | 50 | 50 |
| A. Rodarte | Children’s Hospital, San Diego | 13 | 50 | 25 | 25 |
| E. Sarkis | Sarkis Clinical Trials, Gainesville, FL | 14 | 9 | 4 | 5 |
| B. Finkel | Aeroallergy Research Labs, Savannah, GA | 15 | 55 | 28 | 27 |
| L. Sher | Peninsula Research Associates, CA | 16 | 113 | 57 | 56 |
| Total | | | 535 | 266 | 269 |

b(4)

Source: Study 3-004-1 report Appendix 16.1.4 and ISS dataset DEMOG_D

10.2.11.2 Subject Disposition

Five hundred and four pediatric subjects were to complete the study and be evaluable. A total of 535 subjects were enrolled and treated, representing the ITT population (all 518 that were originally randomized and treated, and 17 of 23-planned replacement subjects exposed to treatment). The LHM group consisted of 269-patients, and the placebo group consisted of 266-patients. Anesiva states that “Over-enrollment was permitted to ensure a balanced age distribution.”

Of the 269 subjects treated with LHM, 86 were ages 3–7 years, 81 were ages 8–12 years, and 102 were ages 13–18 years. Of the 266 subjects treated with placebo, 81 were ages 3–7 years, 81 were ages 8–12 years, and 104 were ages 13–18 years.

Table 10-17 below summarizes enrollment by treatment arm, and by age group.

Table 10-17: Study 3-004-1 Enrollment by Treatment Arm, and by Age Group (ITT)

| | LHM N=269 | Placebo N=266 | Total N=535 |
|-------------------------------|--------------|------------------|----------------|
| Subjects treated ¹ | 269 (100.0) | 266 (100.0) | 535 (100.0) |
| Ages 3–7 years | 86 (32.0) | 81 (30.5) | 167 (31.2) |
| Ages 8–12 years | 81 (30.1) | 81 (30.5) | 162 (30.3) |
| Ages 13–18 years | 102 (37.9) | 104 (39.1) | 206 (38.5) |
| Completed Study | 257 (95.5) | 255 (95.9) | 512 (95.7) |
| Discontinued Study | 12 (4.5) | 11 (4.1) | 23 (4.3) |

¹ Includes initially randomized and replacement subjects

Source: CSR Table 10.1.3, page-61

Efficacy Analysis Sets

All 535 treatment-exposed subjects are included in the ITT population; 517 originally randomized subjects and 18 replacement subjects. The “full analysis set” includes 517 subjects, 260 LHM-treated and 257 placebo-treated, all with Wong-Baker FACES scores recorded following venipuncture or cannulation.

The efficacy evaluable set of 508 subjects, 256 in the LHM group and 252 in the placebo group, included all subjects in the full analysis set except those with failed first attempts at venipuncture, or with “major

protocol deviations.” “Major protocol deviations” were not prospectively defined, however. Nine “full analysis set” subjects were excluded from the efficacy evaluable population. Six of these had failed first attempts at venipuncture. Three were excluded “...because damage to the device label may have exposed the treatment information to subjects or staff.”

Discontinuations

A total of 23 subjects were discontinued from the study: 12 in the LHM group and 11 in the placebo group. One LHM discontinuation (015-5378) was due to withdrawal of consent, one (003-6013) was due to failure to comply with protocol requirements, while the remainder were due to failed first attempt at venipuncture or IV. One discontinuation in the placebo group (003-7030) was due to failure to comply with protocol requirements, while the remainder were due to failed first venipuncture /IV attempt.

All 23 subjects who withdrew or were discontinued were assigned replacements, but only 18 of the 23 replacement subjects were enrolled prior to the close of the study. Of the 18 replacement subjects, 10 (3.7% of all subjects treated) were treated with LHM, and 8 (3.0%) received placebo.

One subject (013-5244) experienced a device failure, but “...was successfully treated with another device and completed the study.” This subject was deemed to have been replaced in error.

Table 10-18 below summarizes the number of subjects in each analysis set, by treatment group.

Table 10-18: Study 3-004-1 Analysis Sets, by Treatment Group

| | LHM N=269 (%) | Placebo N=266 (%) | Total N=535 (%) |
|------------------------|--------------------------------|------------------------------------|----------------------------------|
| Safety/ITT population | 269 (100.0) | 266 (100.0) | 535 (100.0) |
| Randomized subjects | 259 (96.3) | 258 (97.0) | 517 (96.6) |
| Replacement subjects | 10 (3.7) | 8 (3.0) | 18 (3.4) |
| Full analysis set | 260 (96.7) | 257 (96.6) | 517 (96.6) |
| Efficacy evaluable set | 256 (95.2) | 252 (94.7) | 508 (95.0) |

Source: CSR Section-14, Table-10.1.4 and Appendix 16, Listing 1.2

Table 10-19 below summarizes enrollment and completion, by age and by applicant-defined analysis set.

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Table 10-19: Study 3-004-1 Subject Disposition, by Treatment Group and Age

| LHM-Treated Population | Ages 3-7 | | Ages 8-12 | | Ages 13-18 | | All 3-18 | |
|-----------------------------------|-----------------|--------|------------------|--------|-------------------|--------|-----------------|--------|
| | N | (%) | N | (%) | N | (%) | N | (%) |
| ITT Population (exposed) | 86 | (100) | 81 | (100) | 102 | (100) | 269 | (100) |
| Safety Population | 86 | (100) | 81 | (100) | 102 | (100) | 269 | (100) |
| Full analysis set | 80 | (93.0) | 80 | (98.8) | 100 | (98.0) | 260 | (96.7) |
| Efficacy evaluable set | 77 | (89.5) | 80 | (98.8) | 99 | (97.1) | 256 | (95.2) |
| Completed | 78 | (98.8) | 80 | (98.8) | 99 | (97.1) | 257 | (95.5) |
| Discontinued | 8 | (9.3) | 1 | (1.2) | 3 | (2.9) | 12 | (4.5) |
| Protocol Deviation | 0 | (0) | 1 | (1.2) | 0 | (0) | 1 | (0.4) |
| Withdrew consent | 1 | (1.2) | 0 | (0) | 0 | (0) | 1 | (0.4) |
| Other | 7 | (8.1) | 0 | (0) | 3 | (2.9) | 10 | (3.7) |
| Placebo-Treated Population | Ages 3-7 | | Ages 8-12 | | Ages 13-18 | | All 3-18 | |
| | N | (%) | N | (%) | N | (%) | N | (%) |
| ITT Population (exposed) | 81 | (100) | 81 | (100) | 104 | (100) | 266 | (100) |
| Safety Population | 81 | (100) | 81 | (100) | 104 | (100) | 266 | (100) |
| Full analysis set | 80 | (97.7) | 78 | (96.3) | 99 | (95.2) | 257 | (96.6) |
| Efficacy evaluable set | 76 | (94.3) | 78 | (96.3) | 98 | (94.2) | 252 | (94.7) |
| Completed | 78 | (94.3) | 79 | (97.5) | 98 | (94.2) | 255 | (95.9) |
| Discontinued | 3 | (5.7) | 2 | (2.5) | 6 | (5.8) | 11 | (4.1) |
| Protocol Deviation | 0 | (0) | 0 | 0 | 1 | (1.0) | 1 | (0.4) |
| Other | 3 | (4.6) | 2 | (2.5) | 5 | (4.8) | 10 | (3.5) |

Source: Study 3-004-1 report study report Appendix Tables 16.1 and 16.2

10.2.11.3 Protocol Deviations and Violations

Protocol deviations are detailed in data listing 16.2.2.1.4, and in Table 10-20 below. The most common involved minor deviations from the safety assessment schedule, and investigator incorrect categorization of failed first procedure attempts (as deviations). The most prominent deviations were;

- One subject (013-5244) had a device failure, but was then treated with another device, completing the study. This subject was also replaced, in error, by Subject 013-8050, who is also included in the ITT population.
- Three subjects (010-8017, 010-5073, 010-5074) were treated with devices in which damage to the device label may have exposed the treatment information to subjects or staff. These subjects were excluded from the efficacy evaluable population.
- Although assent for all subjects was required by study protocol, some IRBs did not require assent for children, or required assent only for children in specified age ranges. Assent was not collected where it was not required by the IRB.
- Minor consent and assent issues are described for 16 subjects in clinical study report Listing 1.4. These minor issues included a missing witness signature on an assent, missing initials on some or all pages of the informed consent, and incorrect dates. In some cases, informed consent was obtained from non-English-speaking parents or guardians using a translator who signed and dated the “translator” space on the written IRB-approved English consent form.

- Other minor deviations from the protocol included investigator skin assessments, telephone contacts, and pain assessments that were incomplete or performed outside of the protocol-specified schedule, as listed in Listing 1.4, Section 16.

These protocol deviations occurred in similar proportions in the two treatment groups, as shown in Table 10-20 below. Overall, they are unlikely to have impacted study results in any appreciable way. My conclusions regarding the 3-004-1 results would not differ in their absence.

Table 10-20: Study 3-004-1 Protocol Deviations

| Deviation Category | LHM N=269 | | PBO N=266 | | ALL N=535 | |
|---------------------------|----------------------|----------------|----------------------|----------------|----------------------|----------------|
| Informed Consent/Assent | 6 | (2.2%) | 6 | (2.3%) | 12 | (2.2%) |
| Study Entry Criteria | 0 | (0.0%) | 2 | (0.8%) | 2 | (0.4%) |
| Device Problem | 1 | (0.4%) | 1 | (0.4%) | 2 | (0.4%) |
| Visit Schedule | 16 | (5.9%) | 14 | (5.3%) | 30 | (5.6%) |
| Procedures/Tests | 71 | (26.4%) | 75 | (28.2%) | 146 | (27.3%) |
| Randomization | 3 | (1.1%) | 3 | (1.1%) | 6 | (1.1%) |
| Other | 37 | (13.8%) | 39 | (14.7%) | 76 | (14.2%) |
| Non Relevant Deviations* | 53 | (19.7%) | 63 | (23.7%) | 116 | (21.7%) |
| TOTAL | 145 | (53.9%) | 148 | (55.6%) | 293 | (54.8%) |

Source: Applicant response 3/15/2007, ISS dataset DEMOG.XPT

* Includes 21 miscategorized failed first procedure attempts

10.2.12 Demographics/Group Comparability

10.2.12.1 Subject Demographics

Subject baseline demographic characteristics are summarized in Table 10-21 below. Review of these data shows that demographic characteristics were comparable across treatment conditions, though not necessarily representative of the general US population. Subject demographics were similarly comparable across age groups (as evidenced by CSR Tables 14.1.2.2, 14.1.2.3 and 14.1.2.4).

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Table 10-21: Study 3-004-1 Subject Demographics (ITT Population)

| Characteristic | LHM N=269 (%) | Placebo N=266 (%) | All N=535 (%) |
|-----------------------|--------------------------|------------------------------|--------------------------|
| Gender | | | |
| Male (%) | 138 (51.3) | 143(53.8) | 281 (52.5) |
| Female (%) | 131 (48.7) | 123 (46.2) | 303 (47.5) |
| Age (years) | | | |
| Mean ± SD | 10.5 ± 4.4 | 10.7 ± 4.3 | 10.6 ± 4.3 |
| Median | 11.0 | 11.0 | 11.0 |
| Range | 3 – 18 | 3 - 18 | 3 - 18 |
| [3 – 7] | 86 | 81 | 167 |
| [8 – 12] | 81 | 81 | 162 |
| [13 - 18] | 102 | 104 | 206 |
| Ethnicity | | | |
| Caucasian | 189 (70.3) | 175 (65.8) | 364 (68.0) |
| Black | 52 (19.3) | 51 (19.2) | 103 (19.3) |
| Asian | 9 (3.3) | 10 (3.8) | 19 (3.6) |
| Other | 19 (7.1) | 30 (11.3) | 49 (9.2) |
| Weight (kg) | | | |
| Mean ± SD | 41.7 ± 22.9 | 41.9 ± 21.9 | 41.8 ± 22.4 |
| Median | 34.6 | 37.4 | 35.8 |
| Range | 12.7–122.2 | 10.9–126.1 | 10.9–126.1 |

Source: Study 3-004-1 report Tables 11.2.5 and data listings 2.1 (Section-14)

10.2.12.2 Baseline Medical Conditions (Medical History)

Subjects' previous medical history is not described within the text of the study report. In general, subjects were healthy, without chronic disease or significant comorbidities. The most frequent reasons for venipuncture/IV, summarized were roughly equally distributed between treatment groups.

Vital signs were not obtained at screening, nor was laboratory testing done.

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10.2.13 Study 3-004-1 Efficacy Results

10.2.13.1 Primary Efficacy Data

The primary efficacy measure was subjects' assessment of pain, from venipuncture or peripheral venous cannulation performed one to three minutes after drug administration, measured using the Wong-Baker FACES scale, anchored at 0 for "no hurt" and 5 for "hurts worst" for all ages (3–18 years).

Though not specified as the primary analysis, WBF data were compared between treatment groups for the entire ITT population, which included all treated subjects, regardless of whether or not venipuncture was performed, or WBF pain score obtained. Missing WBF scores were imputed to the worst value, "5" = "Hurts Worst".

The results of the ITT analysis are summarized in Table 10-22 below above. Treatment with LHM resulted in statistically significantly ($p = 0.003$) less pain, from venipuncture or IV cannulation, compared with placebo. The difference in LSMs was rather small, however (-0.39 ± 0.13).

Table 10-22: Study 3-004-1 Wong-Baker FACES Score (ITT)

| | LHM (N = 269) | Placebo (N = 266) |
|-------------------------|--------------------------|------------------------------|
| Adjusted Mean, LSM | 1.38 | 1.77 |
| Standard Error of LSM | 0.09 | 0.09 |
| Difference in LSMs (SE) | -0.39 (0.13) | |
| p-value | 0.003 | |
| 95% Confidence Limits | -0.65, -0.13 | |

Source: Study 3-004-1 report Tables 11.1.10 and 5.1.1B in Section-14

The applicant specified as primary, analysis of WBF data for the full analysis population (FAP), all treated subjects (who underwent venipuncture or IV cannulation) with primary efficacy endpoint (WBF score). This population included all originally randomized and replacement subjects. Missing WBF scores, such as those for subjects replaced after unsuccessful venipuncture attempt, were NOT imputed. Data from these subjects were not included in this analysis, summarized in Table 10-23 below. These findings are consistent with those for the ITT population.

Table 10-23: Study 3-004-1 Wong-Baker FACES Score (FAP)

| | LHM (N = 260) | Placebo (N = 257) |
|-------------------------|--------------------------|------------------------------|
| Adjusted Mean, LSM | 1.28 | 1.67 |
| Standard Error of LSM | 0.09 | 0.09 |
| Difference in LSMs (SE) | -0.38 (0.12) | |
| p-value | 0.002 | |
| 95% Confidence Limits | -0.62, -0.14 | |

Source: Study 3-004-1 report Tables 11.1.9 and 5.1.1

10.2.13.2 Key Secondary Efficacy Data

Overall, the analyses of key secondary data support the positive primary efficacy findings.

Subject Assessment of Pain Using 100-mm VAS (Ages 8 – 18)

The treatment difference for subject VAS pain rating (ages 8-18) approaches statistical significance in the ITT population (Table 10-24).

Table 10-24: Study 3-004-1, Subject VAS, Ages 8-18

| | <u>ITT Population</u> | | <u>FAS Population</u> | |
|-------------------------|------------------------|----------------------------|------------------------|----------------------------|
| | LHM (N=183) | Placebo (N=185) | LHM (N=180) | Placebo (N=177) |
| Adjusted Mean, LSM | 16.58 | 21.47 | 15.23 | 18.04 |
| Standard Error of LSM | 1.80 | 1.78 | 1.49 | 1.51 |
| Difference in LSMs (SE) | -4.89 (2.53) | | -2.81 (2.12) | |
| p-value | =0.054 | | =0.186 | |
| 95% Confidence Limits | -9.87, 0.09 | | -6.98, 1.36 | |

Source: Study 3-004-1 report Table 11.1.11 and Appendix Table 5.2.1.B

Parent Assessment of Child’s Pain Using 100-mm VAS (Ages 3 – 18)

The difference between treatment groups for the secondary efficacy measure “Parent Assessment of Child’s Pain on 100-mm VAS” achieves statistical significance for both the ITT and FAS populations, as shown in Table 10-25.

Table 10-25: Study 3-004-1, Parent VAS Assessment of Child’s Pain, Ages 3 to 18

| | <u>ITT Population</u> | | <u>FAS Population</u> | |
|-------------------------|------------------------|----------------------------|------------------------|----------------------------|
| | LHM (N=269) | Placebo (N=266) | LHM (N=260) | Placebo (N=257) |
| Available Data | N=255 | N=254 | N=255 | N=253 |
| Adjusted Mean, LSM | 16.66 | 22.97 | 16.66 | 23.03 |
| Standard Error of LSM | 1.44 | 1.45 | 1.45 | 1.45 |
| Difference in LSMs (SE) | -6.31 (2.04) | | -6.37 (2.05) | |
| p-value | ≈0.002 | | ≈0.002 | |
| 95% Confidence Limits | -10.3, -2.29 | | -10.4, -2.35 | |

Source: Study 3-004-1 report Table 11.1.12 and Appendix Table 5.4.1.B

10.2.13.3 Treatment Effect by Study Center

Anesiva did not present by-center efficacy analyses for Study 3-004-1.

My own analysis, as for Study 3-003-1, was conducted on the primary efficacy measure, the FACES score, for the complete ITT population (the overall primary efficacy analysis). These data show (in Table 10-26 below) that Centers 09, 15 and 16 had primary efficacy results that were considerably better than for the other clinical sites.

Center 09, Johns Hopkins Medical Center, Anesthesiology, enrolled only 27 subjects. Center 16, an independent Contract Research Organization (Peninsula Research Associates, CA) also enrolled the greatest number of Study 3-004-1 subjects, thus was chosen for routine DSI inspection. Center 15, the third site with superior efficacy results, also an independent CRO (Aeroallergy Research Labs, Savannah, GA), with average enrollment (55-enrolled, mean = 59/center), was selected for inspection as well.

Table 10-26: 3-004-1 Treatment Effect by Center

| | N (ITT) | FACES P-Value ^a |
|------------|---------|-------------------------------|
| Center #02 | 2 | NA |
| Center #03 | 106 | 0.783 |
| Center #04 | 73 | 0.346 |
| Center #09 | 27 | 0.005 |
| Center #10 | 100 | 0.507 |
| Center #13 | 50 | 0.301 |
| Center #14 | 9 | 0.461 |
| Center #15 | 55 | 0.129 |
| Center #16 | 113 | 0.146 |
| Overall | 535 | 0.003 |

Source: ^a Clinical reviewer, Oneway ANOVA

10.2.14 Procedure Performed

Venipuncture was performed in 72.1% of subjects, and peripheral vein cannulation was performed in 27.7%. The ACF was the treatment site in 74.2% of subjects, and the BOH was chosen in 25.4%. No differences were apparent between the LHM placebo treatment groups, with respect to procedures performed or anatomic site. These data are summarized in Table 10-27.

Table 10-27: Study 3-004-1 Procedure Performed and Treatment Site (ITT)

| | Number (%) of Subjects | | |
|----------------------------|------------------------|----------------------|--------------------|
| | LHM (N=269) | Placebo (N = 266) | Total (N = 535) |
| Procedure Performed | | | |
| Cannulation | 74 (27.5) | 74 (27.8) | 148 (27.7) |
| Venipuncture | 194 (72.1) | 191 (71.8) | 385 (72.0) |
| Body Site | | | |
| Antecubital fossa (ACF) | 198 (73.6) | 199 (74.8) | 397 (74.2) |
| Back of hand (BOH) | 70 (26.0) | 66 (24.8) | 136 (25.4) |

Source: Study 3-004-1 report, Table 11.2.2.3

Subjects in both treatment groups underwent venipuncture or cannulation with needle sizes ranging from 18– 25 gauge. The distribution of needle sizes was similar in the two treatment arms.

10.2.15 Discussion of Study 3-004-1 Efficacy Findings

The primary efficacy data from Study 3-004-1 provide support for Anesiva's efficacy claim; Zingo™ provides local analgesia when administered on intact skin one to three minutes prior to venipuncture or peripheral intravenous cannulation. As with Study 3-003-1, although the magnitude of treatment effect is relatively small (<0.4 on a 6-point scale), the finding is statistically significant for both the ITT and FAS populations.

Unlike for Study 3-003-1, though, the Study 3-004-1 subject-reported VAS scores (ages 8-18 only) do not provide statistically significant support for the primary efficacy findings. For the ITT population the treatment group difference of less than 5-mm (100-mm VAS) does not reach statistical significance ($p=0.054$). In Study 3-003-1 the subject VAS treatment group difference was ≈ 10 -mm/100-mm, with p -values for both ITT and FAS populations <0.001 .

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10.3 Study 2-002-001 (Pediatric)

Study 2-002-001 was very similar in design to Studies 3-003-1 and 3-004-1 except for:

- Device - The ND5.3 device was utilized, not the final, ND5.3A device
- Population - Only subjects scheduled for back-of-hand venipuncture were enrolled (not IV)
- Primary efficacy measure
 - In 3 to 7 year-olds only the WB-FACES was used
 - In 13 to 18 year-olds only the VAS was used
 - In 8 to 12 year-olds both were used, though neither was designated as “primary”

It was conducted at a single US clinical site between 5/19/2004 and 9/15/2004. The Clinical Study Report was dated 08/11/06.

Efficacy findings, summarized in Table 10-29, Table 10-30 and Table 10-31 *appear to be* moderately supportive, but statistical issues (i.e., multiple primary endpoints, no corrections for multiplicity) raise concerns about the validity and utility of these data.

In total, 306 subjects were exposed:

- 299 were randomized, one of whom was not exposed due to device failure
- Nine subjects were replaced, but
 - Seven of these received study drug and completed the WB-FACES and/or the VAS
- One subject was inadvertently randomized and enrolled twice (Data from the first session only were included in Anesiva’s efficacy analyses, but safety analyses include both)

Table 10-28: Study 2-002-001 Exposure (N=306^a)

| | Active LHM | Placebo |
|----------------|----------------|----------------|
| | 0.50-mg/20-bar | 0.00-mg/20-bar |
| Total | 152 | 155 |
| 3 to 7 years | 51 | 52 |
| 8 to 12 years | 50 | 53 |
| 13 to 18 years | 51 | 50 |

^a307 exposures in 306 subjects Source: Study dataset DEMOG

Table 10-29: Study 2-002-001 Primary Efficacy Results (FAS)

| | Active LHM | Placebo | Effect Size | P-Value* |
|-------------------------|----------------|----------------|-------------|----------|
| | 0.50-mg/20-bar | 0.00-mg/20-bar | | |
| Wong-Baker FACES | | | | |
| 3 to 7 years (N) | 50 | 52 | -0.455 | 0.024 |
| Mean (±SD) | 1.52 (±1.83) | 2.42 (±2.12) | | |
| 8 to 12 years (N) | 50 | 52 | -0.359 | 0.073 |
| Mean (±SD) | 0.98 (±1.13) | 1.40 (±1.22) | | |
| VAS (100-mm) | | | | |
| 8 to 12 years (N) | 50 | 53 | -0.331 | 0.097 |
| Mean (±SD) | 10.90 (±19.96) | 17.86 (±22.06) | | |
| 13 to 18 years (N) | 50 | 50 | -0.463 | 0.023 |
| Mean (±SD) | 14.08 (±18.04) | 23.41 (±22.07) | | |

P-value with 2-sided t-test

Source: CSR Tables 5.1.1, 5.1.2, 5.2.1 and 5.2.2 (Section 15)

Prospectively specified secondary efficacy analyses (in Study 2-002-001) included:

- Two “combined analyses” in all ages combined (3-18 years)
- Two additional “combined analyses,” one in 3 to 12 year-olds (WB-FACES), and one in 8 to 18 year-olds (VAS)
- Parental pain assessment(VAS), in all ages combined

Table 10-30: Study 2-002-001 Secondary Efficacy Results (FAS)

| | Active LHM | | Placebo | Effect Size | P-Value |
|--------------------------------|--------------------------------|--------------------|---------------------------------|-------------|----------|
| | 0.50-mg/20-bar | 0.00-mg/20-bar | | | |
| WB-FACES in 3 to 12 y/o | N=100 | N=104 | | | |
| Mean (±SD) | 1.25 (±1.54) | 1.91 (±1.80) | | -0.396 | 0.004* |
| VAS in 8 to 18 y/o | N=100 | N=103 | | | |
| Mean (±SD) | 12.49 (±19.00) | 20.55 (±22.14) | | -0.395 | 0.005* |
| Parent VAS | N=150 | N=154 | | | |
| All Ages Mean (±SD) | 13.63 (±20.98) | 19.51 (±25.15) | | NA | 0.027 |
| 3 to 7 y/o: Mean (±SD) | 18.04 (±23.97) | 28.15 (±30.69) | | NA | 0.067 |
| 8 to 12 y/o: Mean (±SD) | 12.38 (±20.43) | 15.96 (±22.38) | | NA | 0.400 |
| 13 to 18 y/o: Mean (±SD) | 10.48 (±17.76) | 14.19 (±18.69) | | NA | 0.314 |
| Combined 3 to 18 y/o | WB-FACES in 3 to 12 y/o | 3 to 12 y/o | with VAS in 13 to 18 y/o | | |
| | -- | -- | -- | -0.428 | <0.001** |
| Combined 3 to 18 y/o | WB-FACES in 3 to 7 y/o | 3 to 7 y/o | with VAS in 8 to 18 y/o | | |
| | -- | -- | -- | -0.191 | <0.001** |

*Pairwise ANOVA

**Glass meta-analysis

Source: CSR Tables 11.I, 11.J and 11.K

Several responder analyses were performed, though these had not been described in the statistical analysis plan (or protocol). Findings from these post-hoc analyses appear to be supportive (Table 10-31 below). No corrections were made for multiplicity, however.

Table 10-31: Study 2-002-001 Post-Hoc Responder Analyses

| Response Criteria ^a | Active | Placebo | Odds Ratio (95% CI) | P-Value ^b |
|---------------------------------------|------------------|-----------------|-----------------------|-----------------------|
| WB-FACES Score 0 or 1, OR VAS ≤ 15-mm | 102/150 68.0% | 78/155 50.3% | 2.10 (1.32 – 3.34) | CMH=0.002 LR=0.002 |
| WB-FACES Score 0 or 1 | 71/100 71.0% | 53/105 50.5% | 2.44 (1.36 – 4.36) | CMH=0.003 LR=0.003 |
| WB-FACES Score 0, OR VAS ≤ 15-mm | 73/150 48.7% | 53/155 34.2% | 1.86 (1.16 – 2.98) | CMH=0.010 LR=0.010 |
| WB-FACES Score 0 | 42/100 42.0% | 28/105 26.7% | 1.99 (1.11 – 3.56) | CMH=0.021 LR=0.022 |

^a VAS only in ages 13-18; No WB-FACES scores

^b Cochran-Maentel-Hanzel and logistic regression

Source: 2-002-001 Study Report Tables 15.1A, 15.1B, 15.2A, 15.2B, 16.1A, 16.1B, 16.2A, 16.2B

10.4 Study 4-400-001 (Pediatric)

Study 4-400-001 was a double-blind, placebo-controlled, parallel-group pediatric study conducted at a single clinical site in Poland between 10/29/04 and 01/23/04. Efficacy findings from this double-blind, placebo-controlled, parallel-group pediatric study do not provide support for the applicant's efficacy claim. Furthermore, the integrity of the efficacy data is questionable.

The original CSR, dated 03/31/04, was amended on 06/28/06. The amendment states, "The following sections are incomplete, as the previous sponsor did not provide the information in the report."

- Section 16.1.9, *Documentation of Statistical Methods*
- Section 16.1.10, *Documentation of Inter-Laboratory Standardization Methods and Quality Assurance Procedure*
- Section 16.1.3, *List of IRBs and Representative Written Information for Subject and Sample Consent Forms*: "The name of the independent ethics committee is not listed."

Section-16 is actually missing entirely from the CSR. The subsections listed above are not "incomplete." They do not exist.

Study 4-400-001 was similar to Studies 3-003-1, 3-004-1 and 2-002-001, but incorporated four treatment conditions, as shown in Table 10-32.

Table 10-32: Study 4-400-001 Enrollment by Treatment

| Treatment Group | Enrollment |
|-------------------------|------------|
| Total | 195 |
| 0.5-mg lidocaine/20-bar | 48 |
| 0.5-mg lidocaine/40-bar | 49 |
| Placebo/20-bar | 49 |
| Placebo /40-bar | 49 |

Source: ISS dataset DEMOG-D.XPT

Subjects were grouped by age (3-7, 8-12, and 13-18 years). Treatments were distributed equally, within each age-group (16 or 17 subjects from each age-group, within each treatment condition).

The original protocol (dated 08/03) includes the following description of efficacy endpoints:

- Children in the youngest age group will rank the pain of the venipuncture on the back of the hand using the Wong-Baker FACES pain rating scale (Appendix C)
- Children in the oldest age group will rank the pain of the venipuncture on the back of the hand using the 100 mm VAS (anchored at 0="No pain" and at 100="Extreme pain")
- Children in the middle age group will rank the pain of the venipuncture on the back of the hand by the use of both assessment tools, as a bridge between the oldest and youngest groups.

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The primary efficacy parameter was "...the combined effect size from the three age groups." The combined efficacy analysis was performed in two different ways, both using Glass's meta-analysis, "... since the middle age group used both the Wong- Baker FACES scale and the VAS to report the pain of venipuncture." One method estimated the effect size from the Wong- Baker FACES scores for the youngest and middle age groups, and from the VAS for the oldest age group. The other combined analysis utilized the Wong- Baker FACES scores for the youngest age group, and the VAS scores for the middle and oldest age groups. Results of both analyses are presented in Table 10-33 below. There were no significant differences between the active and placebo treatments.

Table 10-33: Study 4-400-001 Efficacy Analyses

| Pair-Wise Comparison | Effect Size | 95% CI | P-Value |
|--|-------------|-----------------|---------|
| FACES 3 to 12, VAS 13 to 18 | | | |
| Active 0.50-mg/20-bar / Placebo/20-bar | -0.182 | -0.586 to 0.223 | 0.379 |
| Active 0.50-mg/40-bar / Placebo/40-bar | -0.165 | -0.563 to 0.233 | 0.416 |
| FACES 3 to 7, VAS 8 to 18 | | | |
| Active 0.50-mg/20-bar / Placebo/20-bar | -0.297 | -0.702 to 0.108 | 0.151 |
| Active 0.50-mg/40-bar / Placebo/40-bar | -0.087 | -0.486 to 0.313 | 0.670 |

Source: 4-400-001 CSR Section-14, Tables 6.3.1 and 6.3.2 (Table-E, page-40)

Secondary analyses compared differences in mean pain scores between treatment groups, for each age group individually and also for various age group combinations. The results for the youngest and middle groups of subjects, who utilized the Wong-Baker FACES scale, are presented in Table 10-34

Table 10-34: Mean Wong-Baker FACES Scores for 3 to 7, and for 8 to 12 Age Groups

| | ALGRX 3268 0.5 mg/20 bar Mean (N) | 20 bar Sham Mean (N) | 0.5 mg/20 bar- 20 bar Sham Difference in Adjusted Means | P-value* |
|-----------|---|-------------------------|--|----------|
| Ages 3-7 | 0.69 (16) | 1.94 (17) | -1.25 | 0.0191 |
| Ages 8-12 | 0.75 (16) | 0.69 (16) | 0.06 | 0.7965 |
| Ages 3-12 | 0.72 (32) | 1.33 (33) | -0.60 | 0.0415 |
| | ALGRX 3268 0.5 mg/40 bar Mean (N) | 40 bar Sham Mean (N) | 0.5 mg/40 bar- 40 bar Sham Difference in Adjusted Means | P-value* |
| Ages 3-7 | 0.88 (17) | 1.19 (16) | -0.31 | 0.5600 |
| Ages 8-12 | 0.63 (16) | 0.53 (17) | 0.10 | 0.6891 |
| Ages 3-12 | 0.76 (33) | 0.85 (33) | -0.10 | 0.7157 |

Source: Clinical study report, Table F, page-40

The mean VAS score differences (between treatment groups) for the middle group, oldest group, and combined middle and oldest groups are presented in Table 10-35. There were no significant differences between treatment groups. All VAS scores were low, however, including those in placebo-treated subjects, possibly making it difficult to demonstrate a pain reduction with active-drug treatment.

Table 10-35: VAS Pain Scores for 8 to 12 and for 13 to 18 Age Groups

| | ALGRX 3268 0.5 mg/20 bar Mean (N) | 20 bar Sham Mean (N) | 0.5 mg/20 bar- 20 bar Sham Difference in Adjusted Means | P-value* |
|------------|--|---------------------------------|--|-----------------|
| Ages 8-12 | 7.19 (16) | 10.50 (16) | -3.31 | 0.4011 |
| Ages 13-18 | 21.81 (16) | 17.38 (16) | 4.44 | 0.5201 |
| Ages 8-18 | 14.50 (32) | 13.94 (32) | 0.56 | 0.8867 |
| | ALGRX 3268 0.5 mg/40 bar Mean (N) | 40 bar Sham Mean (N) | 0.5 mg/40 bar- 40 bar Sham Difference in Adjusted Means | P-value* |
| Ages 8-12 | 7.75 (16) | 4.59 (17) | 3.16 | 0.4159 |
| Ages 13-18 | 10.00 (16) | 17.13 (16) | -7.13 | 0.3030 |
| Ages 8-18 | 8.88 (32) | 10.67 (33) | -1.98 | 0.6134 |

Source: Clinical study report, Table G, page-41

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10.5 Study 4-401-001 (Pediatric)

Study 4-401-001, conducted at a single clinical site in Poland from 5/09/03 to 7/16/03, was very similar in design to Study 4-400-001. It was a randomized, double-blind, placebo-controlled, single-dose, parallel-group study, enrolling outpatient subjects undergoing scheduled (routine) venipuncture, between the ages of 3 and 18. The original CSR, dated 10/16/03, was amended on 07/05/06.

Efficacy findings, summarized in Table 10-38, do not support the applicant's efficacy claim. As in Study 4-400-001, statistical issues raise concerns about the validity and utility of these data.

The ND5.3 device was evaluated in 145 subjects. There were three treatment conditions, all utilizing 20-bar pressure. As in the other pediatric studies, subjects were grouped by age (3-7, 8-12, and 13-18 years). Treatments were distributed equally, within each age-group (within each treatment condition, there were 16 or 17 subjects from each of the three age-groups). Treatment conditions, and study enrollment are summarized in Table 10-36.

Table 10-36: Study 4-401-001 Enrollment by Treatment and by Age-Group

| Treatment Group | Enrollment | Ages 3 to 7 | Ages 8 to 12 | Ages 13 to 18 |
|--------------------------|------------|-------------|--------------|---------------|
| Total | 145 | 49 | 48 | 48 |
| 0.25-mg lidocaine/20-bar | 48 | 16 | 16 | 16 |
| 0.50-mg lidocaine/20-bar | 48 | 16 | 16 | 16 |
| Placebo/20-bar | 49 | 17 | 16 | 16 |

Source: ISS dataset DEMOG-D.XPT

The primary efficacy measure, subjects' assessment of venipuncture-induced pain, was assessed differently, depending upon subject age. Assessment instruments to be used for the primary analysis were prospectively specified in the protocol as listed in Table 10-37.

Table 10-37: Study 4-401-001 Primary Efficacy Instruments

| Age Group | Primary Measure(s) |
|-----------|-------------------------------|
| 3 - 7 | Modified FACES |
| 8 - 12 | Modified FACES AND 100-mm VAS |
| 13 - 18 | 100-mm VAS |

Source: Clinical reviewer

The primary efficacy analysis calculated the combined treatment effect for all age groups. "Because the age groups utilized different rating scales to report the pain of venipuncture, two primary analyses were run on LHM-0.5 mg compared to placebo, and on LHM-0.25 mg compared to placebo."

- In one analysis, the effect size was estimated from the modified FACES scores in the youngest and middle age groups, and from the VAS scores for the oldest age group.
- The other analysis compared the effect size as estimated from the modified FACES scores in the youngest age group, and from the VAS scores in the middle and oldest age groups.

Results from Anesiva's analyses are summarized in Table 10-38 below.

Table 10-38: Study 4-401-001 Efficacy Analyses

| Pair-Wise Comparison | Effect Size | 95% CI | P-Value |
|------------------------------------|-------------|------------------|---------|
| <u>FACES 3 to 12, VAS 13 to 18</u> | | | |
| Active 0.50-mg / Placebo | -0.389 | -0.793 to -0.016 | 0.0598 |
| Active 0.25-mg / Placebo | -0.325 | -0.728 to 0.079 | 0.1145 |
| Active 0.25-mg / Active 0.50-mg | 0.083 | -0.321 to 0.486 | 0.6883 |
| <u>FACES 3 to 7, VAS 8 to 18</u> | | | |
| Active 0.50-mg / Placebo | -0.428 | -0.834 to -0.022 | 0.0389 |
| Active 0.25-mg / Placebo | -0.382 | -0.786 to 0.022 | 0.0635 |
| Active 0.25-mg / Active 0.50-mg | 0.024 | -0.378 to 0.426 | 0.9082 |

Source: 4-401-001 CSR Section-14, Tables 6.3.1 and 6.3.2 (Table-E, page-38)

Anesiva considers these findings evidence that, “Subjects of all ages combined receiving LHM-0.5 mg had statistically significantly lower pain scores than subjects receiving placebo.”

A secondary efficacy analysis tabulated the treatment effects within each age group. Treatment effect was estimated using an ANOVA with treatment, age and age-by-treatment interaction effects.

Efficacy Results: Subjects of all ages combined receiving LHM-0.5 mg had statistically significantly lower pain scores than subjects receiving placebo. The combined effect size, across age groups, was estimated using the modified FACES scores for the 3 to 7 group, and the VAS scores for the middle and oldest age groups. The estimated effect size was (-0.428), with a p-value=0.039.

Using the same analysis, a non-statistically significant treatment effect was seen subjects receiving LHM-0.25 mg as compared to placebo (effect size -0.382, p=0.0635).

The analysis that utilized the modified FACES scores for the youngest and middle groups, and VAS scores for the oldest group showed a non statistically significant difference between treatment groups (LHM-0.5 mg vs. placebo; -0.389, p=0.0598). Anesiva contends that:

It was discovered during the study that the youngest children had difficulty discerning the faces of the modified FACES scale, even though all of the children had been able to discern the faces of the modified FACES scale during the screening period. Therefore, the VAS scores were considered to be more reflective of treatment effect than the modified FACES scale.

Multiplicity issues are not addressed in the protocol, or in the Clinical Study Report.

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10.6 Study 1-102-1 (Adult)

Study 1-102-001, conducted between 06/23/03 and 07/16/03 at a single US site, was a double-blind, placebo-controlled, within-subject, two-period crossover, dose-ranging study, enrolling adult volunteers. The original CSR was dated 12/15/03, with an amended CSR dated 06/28/06.

Overall, the Study 1-102-001 data do not provide support for the proposed efficacy claim, for the to-be-marketed dose (lidocaine 0.50-mg/21-bar). Anesiva's primary efficacy analysis was performed on the 'efficacy evaluable' population, which omitted nearly 13% of treated subjects. Still, no statistically significant treatment difference (from placebo) was shown, for the lidocaine 0.50-mg/20-bar treatment.

Methodological and statistical issues aside, The Study 1-102-001 data *may* suggest that a 1 to 3-minute treatment-to-venipuncture (TTV) interval may be better than longer intervals (5 or 10-minutes).

Two device pressures (20-bar and 40-bar), and four different treatment-to-venipuncture (TTV) intervals (1, 3, 5 and 10-minutes) were evaluated. Each subject was to receive two single doses, one week apart (lidocaine 0.50-mg and placebo). Of the 183 subjects enrolled, 91 were randomized to receive 20-bar treatments, and 92 were randomized to receive 40-bar treatments. Each subject was assigned to one of four TTV intervals; 1, 3, 5 or 10-minutes. The primary efficacy measure was subjects' assessment of venipuncture pain, using 100-mm VAS.

In the 40-bar group (Group-2), for all TTV intervals combined, VAS scores (Table 10-39) were statistically significantly lower after active-drug treatment than after placebo (-5.7-mm difference, p=0.043). For 20-bar subjects (Group-1), the corresponding VAS difference was (-2.7)-mm (p=0.364).

Table 10-39: Study 1-102-1 Applicant's Primary Efficacy Findings (Efficacy Evaluable Population)

| Treatment Group | N | Mean SE | Median | Range | 95% CI | P-Value |
|-------------------------------|----|-------------|--------|---------|----------------|---------|
| <u>0.50-mg/20-bar vs. PBO</u> | | | | | | |
| Total | 79 | -2.7 ± 3.0 | -3.0 | -54, 77 | (-8.7, +3.2) | 0.364 |
| 1-min | 20 | -12.7 ± 4.7 | -7.0 | -54, 23 | (-22.4, -3.0) | 0.013 |
| 3-min | 19 | 4.6 ± 7.5 | +3.0 | -40, 77 | (-11.0, +20.3) | 0.542 |
| 5-min | 20 | -5.1 ± 4.9 | -3.0 | -46, 35 | (-15.3, +5.2) | 0.315 |
| 10-min | 20 | 2.5 ± 6.4 | +2.5 | -42, 70 | (-11.0, +16.0) | 0.702 |
| <u>0.50-mg/40-bar vs. PBO</u> | | | | | | |
| Total | 80 | -5.7 ± 2.7 | -3.5 | -72, 48 | (-11.2, -0.2) | 0.043 |
| 1-min | 20 | -11.8 ± 6.3 | -4.0 | -72, 44 | (-25.1, +1.5) | 0.079 |
| 3-min | 20 | -2.3 ± 5.0 | -2.0 | -48, 39 | (-12.8, +8.2) | 0.653 |
| 5-min | 20 | -4.6 ± 5.1 | ±0.0 | -67, 28 | (-15.4, +6.2) | 0.383 |
| 10-min | 20 | -4.1 ± 5.5 | -9.5 | -51, 48 | (-15.7, +7.5) | 0.468 |

Source: Table 14.1, 1-102-001 CSR

For both 20-bar and 40-bar subjects, mean VAS score differences (between active and placebo) were greatest when the TTV interval was only 1-minute. With the 1-minute TTV interval, mean VAS

differences between active and placebo were (-12.7)-mm and (-11.8)-mm, in the 20-bar and 40-bar groups, respectively. For the 3, 5 and 10-minute intervals, differences were (+4.6), (-5.1) and (+2.5) in Group-1, and (-2.3), (-4.6) and (-4.1)

Anesiva reports that 160 subjects completed the trial.

- One of these, subject #0113 (20-bar, 3-minutes), was excluded because he underwent one of his two venipunctures one-minute after treatment.
- "Therefore, the efficacy evaluable population included 159 subjects, 79 in Group-1, and 80 in Group-2."

Study dropouts were defined as:

- Any subject who discontinued participation in the study prior to the completion of the two treatment days
- Any subjects who did not have "clean" venipunctures on both treatment days
- Any subject who missed one of the two treatment days
- "Any subject who had an AE which the investigator determined should cause the subject to discontinue the study."

The "Multiple Comparisons/Multiplicity" section of the Clinical Study Report states "This section is not applicable to this report."

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10.7 Study 1-100-1 (Adult)

Study 1-100-001, conducted between 09/04/02 and 10/22/02 at a single US site, was a double-blind, placebo-controlled, two-period crossover, dose-ranging study, enrolling 272 adult volunteers. The original CSR was dated 13/27/03, with an amended CSR dated 07/03/06.

In addition to device pressure (20-bar and 40-bar) and lidocaine dose (0.25-mg and 0.50-mg), eight different treatment-to-venipuncture intervals were studied (1, 3, 5, 10, 15, 20, 30 and 60-minutes). The primary efficacy measure was subjects' rating of venipuncture-induced pain, using 100-mm VAS.

Each subject was treated at two single-dose sessions at least one-week apart, with:

- One of the three active-drug configurations listed Table 10-40 below, to the ACF, and with
- A pressure-matched placebo device, to the contralateral ACF (placebo/20-bar, or placebo/40/bar)

Table 10-40: Study 1-100-1 Treatment Arms

| Treatment | N | Dose (mg) | Pressure (bar) |
|--------------|----|-----------|----------------|
| Group-1 (1R) | 80 | 0.25 | 20 |
| Group-2 (2R) | 80 | 0.50 | 20 |
| Group-3 (3R) | 80 | 0.50 | 40 |

Each subject's venipunctures were performed at one of eight post-treatment timepoints (10 subjects per timepoint): 1 min, 3 min, 5 min, 10 min, 15 min, 20 min, 30 min and 60 min.

The applicant's efficacy analyses were not necessarily appropriate given the study design (24 separate pairwise comparisons (ANOVA)), and failed to correct for multiplicity. Furthermore, the primary analysis was performed only on the 'efficacy evaluable' population, omitting nearly 12% of treated subjects. Still, findings (Table 10-41 Table 10-42 below) appear to suggest, that for the ND5.3 device:

- Lidocaine 0.50-mg is more effective than lidocaine 0.25-mg
- 40-bar pressure is more effective than 20-bar pressure
- For all three treatment groups:
 - Onset of dermal analgesia is rapid (one to three minutes post-treatment)
 - By the ten-minute timepoint (post-treatment), differences between active drug and placebo are markedly diminished

Table 10-41: VAS Score after Venipuncture, by Lidocaine Dose and Device pressure (All Timepoints)

| Treatment Group | Mean ± SE | Median | Range | 95% CI | P-Value |
|-----------------------------------|-------------|--------|-------------|-------------|---------|
| Active 0.25mg/20-bar (1R) vs. PBO | -7.4 ± 3.1 | -6.0 | (-83) to 71 | -13.6, -1.1 | 0.0217 |
| Active 0.50mg/20-bar (2R) vs. PBO | -8.2 ± 3.2 | -5.0 | (-91) to 61 | -14.7, -1.8 | 0.0129 |
| Active 0.50mg/40-bar (3R) vs. PBO | -10.3 ± 2.6 | -5.5 | (-80) to 41 | -15.4, -5.1 | 0.0002 |
| Group 1R vs. Group 2R | 0.9 ± 4.2 | NA | NA | -7.5, 9.2 | 0.8344 |
| Group 1R vs. Group 3R | 2.9 ± 4.2 | NA | NA | -5.5, 11.3 | 0.4928 |
| Group 2R vs. Group 3R | 2.0 ± 4.2 | NA | NA | -6.3, 10.4 | 0.6356 |

Source: Study 1-100-001 CSR, Table-9, page-34

Table 10-42: VAS Score after Venipuncture, by Time to Venipuncture; Treatment Group Difference versus Placebo (Mean ± SE / (Range))

| Treatment Group | N | 1-Min | 3-Min | 5-Min | 10-Min | 15-Min | 20-Min | 30-Min | 45-Min |
|---------------------------|------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Active 0.25mg/20-bar (1R) | (10) | -7.8 ± 5.9 | -5.7 ± 13.5 | -17.7 ± 9.8 | -10.5 ± 6.7 | +4.5 ± 7.4 | -9.7 ± 11.1 | -8.2 ± 10.1 | -3.7 ± 4.5 |
| | | (-21.2, 5.6) | (-36.3, 24.9) | (-39.9, 4.5) | (-25.7, 4.7) | (-12.3, 21.3) | (-34.9, 15.5) | (-31.0, 14.6) | (-13.8, 6.4) |
| Active 0.50mg/20-bar (2R) | (10) | -17.7 ± 13.3 | -17.1 ± 13.3 | -15.5 ± 8.1 | +0.0 ± 6.4 | -1.3 ± 7.8 | -15.0 ± 7.4 | -0.1 ± 6.4 | +1.0 ± 11.7 |
| | | (-41.3, 5.9) | (-47.1, 12.9) | (-33.7, 2.7) | (-14.5, 14.5) | (-18.6, 16.0) | (-31.8, 1.8) | (-15.6, 15.4) | (-26.0, 28.0) |
| Active 0.50mg/40-bar (3R) | (10) | -13.4 ± 4.8* | -23.3 ± 9.1* | -15.7 ± 9.9 | +3.3 ± 4.6 | +3.3 ± 4.6 | -10.2 ± 7.2 | -10.3 ± 8.3 | -0.6 ± 4.1 |
| | | (-24.3, -0.3) | (-44.0, -2.6) | (-38.1, 6.7) | (-7.1, 13.7) | (-27.7, 4.1) | (-26.6, 6.2) | (-29.1, 8.5) | (-9.9, 8.7) |
| Groups 1R and 2R combined | (20) | -12.8 ± 5.9 | -11.4 ± 9.3 | -16.6 ± 6.2* | -5.3 ± 4.7 | -5.3 ± 4.7 | -12.4 ± 6.5 | -4.2 ± 6.0 | -1.5 ± 4.1 |
| | | (-25.2, -0.3) | (-30.9, 8.1) | (-29.5, -3.7) | (-15.0, 4.5) | (-9.6, 12.5) | (-26.1, 1.4) | (-16.7, 8.4) | (-13.8, 10.9) |

* p < 0.05, no multiplicity correction
 Bolded = greatest mean difference (active to placebo) for each treatment group

Source: Study 1-100-001 CSR, Table-10, page-36 and Table 6.1 in Section-14

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 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

11 APPENDIX TWO: LABELING REVIEW

The proposed Package Insert (PI) was submitted in Structured Product Labeling (SPL) format, in accordance with the Physician Labeling Rule (PLR). It appears in its entirety, beginning on the following page.

Most label sections are reproduced verbatim, or in large part, from the Synera™ and/or LIDODERM® Package Inserts (the two reference listed drugs for this 505(b)(2) application). These include *Contraindications, Warnings and Precautions, Drug Interactions, Use in Specific Populations, Drug Abuse and Dependence and Overdosage, Clinical Pharmacology and Nonclinical Toxicology.*

Review of the proposed PI (to follow as a separate document) focuses primarily on the clinically-related sections, recommending revisions and additions which may not match the precise wording for the final label, should the product be approved.

Key SEALD Recommendation

- "... since a modified version of the Wong-Baker FACES scale is utilized in the clinical trials, it is inaccurate for the sponsor to refer to the scale by this name in labeling. If efficacy statements concerning this modified instrument are included in the label, a more generic description (i.e. faces pain scale) should be considered."

Key DDMAC Recommendations

- Deletion of the claim Γ \perp from the established name and throughout the PI. While accurate, this is extremely promotional in tone as it is an implied superiority claim. **b(4)**
- Deletion from *Indications and Usage* of the claim, Γ **b(4)**
- Revision of the *Dosage Forms and Strengths* section, to present only the appropriate information.
- Include in the *Warnings and Precautions* section, for consistency with the Synera™ PI, the following statement; Γ **b(4)**
- In the *Adverse Reactions* and *Clinical Studies* sections:
 - Deletion of repetitive, promotional text discussing primary and secondary efficacy measures.
 - Deletion of references to (and claims of) Γ \perp **b(4)**
 - Provision of context for wording such as Γ \perp in the safety discussion, and throughout the PI.
 - Deletion of the word --- in the discussion of skin findings, because it is promotional in tone and, minimizes the risks.

Additional Points

- Only the data from pediatric studies will be presented in the *Clinical Studies* section, and used for calculation of rates of common adverse event and skin findings. Approval for use in adults is not possible at this time, given the lack of adult efficacy data.
- No patients under three years of age were exposed; only seven \geq 65-years were.

12 TABLES AND REFERENCES

12.1 Summary of Clinical Information Requests

Table 12-1: Information Requests and Application Amendments (All Dates in 2007)

| Seq. # | Request | Date | Receipt | Content |
|--------|----------------|-------|---------|--|
| 1 | 12/10 | 01/07 | 01/09 | Revised/corrected datasets (predominantly ISS) |
| Filing | Date | 1/23 | | |
| 2 | 12/10 | 03/02 | 03/08 | Revised safety datasets, include all required data (i.e., no unique PIDs, ISS lacks treatment and demographic information, etc.) |
| 3 | 02/26 | 03/12 | 03/16 | Tabular summaries, by study and treatment, of protocol deviations |
| 4 | | 04/13 | 04/18 | Revised draft labeling |
| 5 | 04/19 | 05/03 | 05/10 | - Statements of certification as required by CFR 314.52 (b) - Documentation of receipt of notice by each person provided the notice as required by CFR 314.52 (e) - Patent information for _____ |
| 6 | 04/20 | 05/17 | 05/22 | ISS for early-device studies (inadequate) |
| 7 | 06/04 06/11 | 06/15 | 06/19 | ISS for early-device studies (acceptable) |
| 8 | NA | 06/22 | 06/27 | Six-month stability data, additional info re: patent certifications |

b(4)

Source: Clinical reviewer

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Table 12-2: Early-Device Studies (Phase-1)

| Study No. | Objectives | Design / Control | Device / Dosage / Route | Number | Subjects or Patients | Treatment |
|-------------|---|---|---|---|---|---|
| C96-101-01 | Safety, efficacy | R, DB, PBO-controlled | ND1 3 mg/30 bar left and right arms | 14 | Healthy subjects, 18-22 years old | Single treatment |
| DPJ-01-001 | Dose ranging | R, DB, PBO-controlled, 3-periods | ND1 2 mg, 3 mg, 5 mg 40 bar or 60 bar at BOH | 18 | Healthy adult male Caucasians | Periods 1 and 2; 4 sites per subject Period 3; 6 sites per subject |
| MDS-20643 | Tolerability, efficacy | R, DB, PBO-controlled, 2-periods | ND1 3 mg/40 bar inner aspect of each arm | 20 | Healthy adult males Caucasian and Black | Two sessions |
| ICR-012770 | Tolerability, efficacy | R, DB, PBO-controlled | ND1 3 mg 40, 60, 80 bar 5 skin sites | Session 1; 18 Session 2; 17 | Healthy adults | Single session 3-treatments |
| D4115-001 | Correlation between skin blood flow and analgesia | Observer blind, PBO-controlled. Skin blood flow measured by Doppler | ND1 3 mg at 40 bar left and right arms | 8 | Healthy adult males | 3-sessions 1-treatment/session |
| DPJ 01-003 | Tolerability | R, DB, PBO-controlled | ND1 3 mg 40, 50 bar at ACF 60 bar at BOH | Visit 1; 30 Visit 2; 29 Visit 3; 29 | Healthy adults Caucasians | Single session 3-treatments |
| ICR-013727 | Tolerability, efficacy | R, SB, PBO-controlled | ND5.1 3 mg at 30 bar ACF and BOH | 40 | Healthy adults | Single session |
| D4115-023 | Tolerability, efficacy | R, SB, PBO-controlled, 2-periods | ND5.1 3 mg / 30 bar 10 µm and 20 µm "different body sites" | 40 | Healthy adults | 2- sessions 7-days apart |
| DPJ-01-004 | Tolerability, efficacy | R, DB, PBO-controlled, own-controlled each subject treated X6 | ND5.2 3 mg, 20 bar ACF | 40 | Healthy adults Caucasians | Single session 6-treatments 2-doses |
| DPJ-LID-009 | Tolerability, efficacy | R, DB, PBO-controlled, own-controlled | ND5.2 0.5, 1 and 2 mg at 25-bar 1 mg at 20, 25 and 30 bar ACF | 20 | Healthy adults | Single session |

Table 12-2: Early-Device Studies (Phase-1)

| Study No. | Objectives | Design / Control | Device / Dosage / Route | Number | Subjects or Patients | Treatment |
|------------|---|---|--|--|---|--------------------|
| DPJ-01-005 | Tolerability, efficacy | R, DB, PBO-controlled, 2-periods | ND5.2 0.5mg/30µm/20bar 0.5mg/40µm/20bar 0.5mg/30µm/25bar 0.5mg/40µm/25bar 1mg/30µm/20bar 1mg/40µm/20bar 1mg/30µm/25bar 1mg/40µm/25bar ACF | Period one: 20 Period two: 80 | Healthy adults | 5 weeks to 7 weeks |
| DPJ-01-002 | Tolerability, efficacy | R, DB, PBO-controlled, own-control | ND1 3 mg at 40 bar; right and left antecubital fossa veins ND1 3mg/30bar/<38µm 3mg/30bar/38-53µm, 3mg/40bar/<38µm, 3mg/40bar/38-53µm; antecubital fossa and back-of-hand, | ITT=40 PP=39 | Adult transplant out-patients | Single session |
| ICR-031091 | Determine which 4-activation conditions offer safety/efficacy | R, SB, PBO-controlled, ascending pressure | ND1 3mg/30bar/<38µm, 3mg/30bar/38-53µm, 3mg/40bar/<38µm, 3mg/40bar/38-53µm; antecubital fossa and back of hand | 116 enrolled 106 evaluable | Patients ages 4-14 years, undergoing venipuncture Caucasian and Asians | Single dose |
| ICR-031086 | Determine which 4-activation conditions offer safety/efficacy | R, SB, PBO-controlled, ascending pressure | ND1 3mg/30bar/<38µm, 3mg/30bar/38-53µm, 3mg/40bar/<38µm, 3mg/40bar/38-53µm; antecubital fossa and back of hand | 132 enrolled 125 evaluable 121 completed | Patients ages 4-14 years, undergoing IV cannulation Caucasians | Single session |

Source: ISS Table 3.1.2

| Table 12-3: Number (%) of Subjects w/ TEAEs Occurring in ≥0.5% in any Treatment Group, Early-Device | | | | | | |
|--|-------------------------------|-----------------------------------|------------------------------------|-------------------------------|--------------------------------|-------------------------------|
| WHO-ART SOC/ Preferred Term | 0.50-mg/ 20-25-bar | >0.50-mg/ 20-25-bar | >0.50-mg/ >25-bar | Placebo/ 20-25-bar | Placebo/ >25-bar | Mannitol (Placebo) |
| | N=60 | N=110 | N=400 | N=140 | N=202 | N=106 |
| Number of subjects w/ any AE | 27 (45.0%) | 73 (66.4%) | 187 (46.8%) | 58 (41.4%) | 53 (26.2%) | 62 (58.5%) |
| Number of subjects w/ no AE | 33 (55.0%) | 37 (33.6%) | 213 (53.3%) | 82 (58.6%) | 149 (73.8%) | 44 (41.5%) |
| Application site disorders | | | | | | |
| Application site oedema | 1 (1.7%) | 0 | 2 (0.5%) | 0 | 1 (0.5%) | 0 |
| Application site reaction | 0 | 0 | 0 | 0 | 2 (1.0%) | 0 |
| Device complication | 0 | 0 | 0 | 1 (0.7%) | 0 | 0 |
| Injection site bleeding | 0 | 5 (4.5%) | 6 (1.5%) | 3 (2.1%) | 0 | 0 |
| Injection site bruising | 5 (8.3%) | 30 (27.3%) | 19 (4.8%) | 23 (16.4%) | 11 (5.4%) | 0 |
| Injection site inflammation | 0 | 0 | 7 (1.8%) | 0 | 0 | 0 |
| Injection site pain | 0 | 6 (5.5%) | 0 | 2 (1.4%) | 0 | 0 |
| Injection site reaction | 0 | 7 (6.4%) | 41 (10.3%) | 5 (3.6%) | 4 (2.0%) | 29 (27.4%) |
| Insertion site pain | 4 (6.7%) | 9 (8.2%) | 5 (1.3%) | 0 | 0 | 0 |
| Insertion site reaction | 1 (1.7%) | 4 (3.6%) | 1 (0.3%) | 1 (0.7%) | 0 | 0 |
| Autonomic NS disorders | | | | | | |
| Syncope | 0 | 1 (0.9%) | 1 (0.3%) | 1 (0.7%) | | |
| Body as a whole – general | | | | | | |
| Allergic reaction | 0 | 0 | 1 (0.3%) | 0 | 1 (0.5%) | 0 |
| Back pain | 0 | 0 | 2 (0.5%) | 0 | 0 | 2 (1.9%) |
| Face oedema | 0 | 0 | 1 (0.3%) | 0 | 0 | 1 (0.9%) |
| Fatigue | 1 (1.7%) | 2 (1.8%) | 2 (0.5%) | 2 (1.4%) | 0 | 2 (1.9%) |
| Headache | 0 | 0 | 8 (2.0%) | 0 | 5 (2.5%) | 2 (1.9%) |
| Influenza-like symptoms | 1 (1.7%) | 2 (1.8%) | 4 (1.0%) | 2 (1.4%) | 2 (1.0%) | 2 (1.9%) |
| Oedema | 0 | 0 | 0 | 0 | 0 | 1 (0.9%) |
| Pain | 0 | 1 (0.9%) | 6 (1.5%) | 1 (0.7%) | 0 | 6 (5.7%) |
| Cardiovascular - general | | | | | | |
| Hypertension | 0 | 0 | 1 (0.3%) | 0 | 1 (0.5%) | 1 (0.9%) |
| Hypotension | 0 | 0 | 0 | 0 | 1 (0.5%) | 0 |
| CNS/PNS D/Os | | | | | | |
| Dizziness | 0 | 3 (2.7%) | 5 (1.3%) | 3 (2.1%) | 1 (0.5%) | 2 (1.9%) |
| Headache | 5 (8.3%) | 15 (13.6%) | 11 (2.8%) | 15 (10.7%) | 1 (0.5%) | 5 (4.7%) |
| Hypoaesthesia | 1 (1.7%) | 1 (0.9%) | 0 | 1 (0.7%) | 0 | 2 (1.9%) |
| Migraine | 0 | 1 (0.9%) | 2 (0.5%) | 1 (0.7%) | 0 | 1 (0.9%) |
| Paraesthesia | 1 (1.7%) | 1 (0.9%) | 1 (0.3%) | 1 (0.7%) | 0 | 2 (1.9%) |
| Gastrointestinal D/Os | | | | | | |
| Abdominal pain | 0 | 1 (0.9%) | 4 (1.0%) | 1 (0.7%) | 2 (1.0%) | 0 |
| Colitis ulcerative aggravated | 0 | 0 | 0 | 0 | 1 (0.5%) | 0 |
| Dyspepsia | 0 | 2 (1.8%) | 3 (0.8%) | 2 (1.4%) | 1 (0.5%) | 1 (0.9%) |
| Nausea | 1 (1.7%) | 1 (0.9%) | 4 (1.0%) | 1 (0.7%) | 1 (0.5%) | 1 (0.9%) |
| Toothache | 0 | 1 (0.9%) | 3 (0.8%) | 1 (0.7%) | 1 (0.5%) | 1 (0.9%) |
| Vomiting | 0 | 0 | 3 (0.8%) | 0 | 0 | 2 (1.9%) |

| Table 12-3: Number (%) of Subjects w/ TEAEs Occurring in ≥0.5% in any Treatment Group, Early-Device | | | | | | |
|--|-------------------------------|-----------------------------------|------------------------------------|-------------------------------|--------------------------------|-------------------------------|
| WHO-ART SOC/ Preferred Term | 0.50-mg/ 20-25-bar | >0.50-mg/ 20-25-bar | >0.50-mg/ >25-bar | Placebo/ 20-25-bar | Placebo/ >25-bar | Mannitol (Placebo) |
| Hearing and vestibular D/Os | | | | | | |
| Earache | 0 | 0 | 2 (0.5%) | 0 | 1 (0.5%) | 0 |
| Heart rate and rhythm D/Os | | | | | | |
| Palpitation | 0 | 0 | 1 (0.3%) | 0 | 0 | 1 (0.9%) |
| Tachycardia | 0 | 0 | 0 | 0 | 1 (0.5%) | 0 |
| Liver/biliary system D/Os | | | | | | |
| SGPT increased | 0 | 0 | 1 (0.3%) | 0 | 1 (0.5%) | 0 |
| Metabolic/nutritional D/Os | | | | | | |
| Ketosis | 0 | 0 | 0 | 0 | 1 (0.5%) | 0 |
| Musculoskeletal D/Os | | | | | | |
| Back pain | 1 (1.7%) | 2 (1.8%) | 0 | 2 (1.4%) | 0 | 0 |
| Bursitis | 1 (1.7%) | 1 (0.9%) | 0 | 1 (0.7%) | 0 | 0 |
| Myalgia | 0 | 1 (0.9%) | 0 | 1 (0.7%) | 0 | 0 |
| Skeletal pain | 0 | 1 (0.9%) | 0 | 1 (0.7%) | 0 | 0 |
| Other AEs | | | | | | |
| Accidental injury | 0 | 0 | 4 (1.0%) | 0 | 1 (0.5%) | 1 (0.9%) |
| Platelet/bleeding/clotting | | | | | | |
| Purpura | 2 (3.3%) | 15 (13.6%) | 82 (20.5%) | 5 (3.6%) | 8 (4.0%) | 24 (22.6%) |
| Psychiatric D/Os | | | | | | |
| Agitation | 0 | 0 | 1 (0.3%) | 0 | 1 (0.5%) | 0 |
| Somnolence | 0 | 0 | 1 (0.3%) | 0 | 0 | 1 (0.9%) |
| Resistance mechanism D/Os | | | | | | |
| Herpes simplex | 0 | 0 | 1 (0.3%) | 0 | 0 | 1 (0.9%) |
| Infection | 0 | 0 | 3 (0.8%) | 0 | 1 (0.5%) | 0 |
| Infection bacterial | 0 | 0 | 3 (0.8%) | 0 | 0 | 0 |
| Infection viral | 0 | 0 | 3 (0.8%) | 0 | 0 | 2 (1.9%) |
| Pharyngitis | 0 | 0 | 5 (1.3%) | 0 | 3 (1.5%) | 1 (0.9%) |
| Respiratory system D/Os | | | | | | |
| Asthma | 0 | 0 | 0 | 0 | 1 (0.5%) | 0 |
| Coughing | 0 | 1 (0.9%) | 2 (0.5%) | 1 (0.7%) | 2 (1.0%) | 1 (0.9%) |
| Pharyngitis | 2 (3.3%) | 3 (2.7%) | 1 (0.3%) | 3 (2.1%) | 1 (0.5%) | 0 |
| Respiratory disorder | 0 | 0 | 2 (0.5%) | 0 | 0 | 2 (1.9%) |
| Rhinitis | 4 (6.7%) | 5 (4.5%) | 12 (3.0%) | 5 (3.6%) | 3 (1.5%) | 6 (5.7%) |
| Sinusitis | 0 | 0 | 1 (0.3%) | 0 | 0 | 1 (0.9%) |
| Upper respiratory infection | 1 (1.7%) | 8 (7.3%) | 1 (0.3%) | 8 (5.7%) | 0 | 0 |
| Secondary terms | | | | | | |
| Cyst NOS | 0 | 0 | 1 (0.3%) | 0 | 0 | 1 (0.9%) |
| Food poisoning | 0 | 0 | 1 (0.3%) | 0 | 1 (0.5%) | 0 |
| Inflicted injury | 0 | 7 (6.4%) | 5 (1.3%) | 7 (5.0%) | 0 | 2 (1.9%) |
| Procedural site reaction | 0 | 0 | 2 (0.5%) | 0 | 0 | 3 (2.8%) |
| Transplant rejection | 0 | 0 | 1 (0.3%) | 0 | 0 | 1 (0.9%) |

| Table 12-3: Number (%) of Subjects w/ TEAEs Occurring in ≥0.5% in any Treatment Group, Early-Device | | | | | | |
|--|-------------------------------|-----------------------------------|------------------------------------|-------------------------------|--------------------------------|-------------------------------|
| WHO-ART SOC/ Preferred Term | 0.50-mg/ 20-25-bar | >0.50-mg/ 20-25-bar | >0.50-mg/ >25-bar | Placebo/ 20-25-bar | Placebo/ >25-bar | Mannitol (Placebo) |
| Skin and appendage D/Os | | | | | | |
| Bullous eruption | 0 | 0 | 0 | 0 | 0 | 1 (0.9%) |
| Pigmentation abnormal | 0 | 5 (4.5%) | 0 | 0 | 0 | 0 |
| Pruritus | 4 (6.7%) | 5 (4.5%) | 8 (2.0%) | 3 (2.1%) | 4 (2.0%) | 0 |
| Rash | 0 | 0 | 2 (0.5%) | 0 | 1 (0.5%) | 0 |
| Rash erythematous | 2 (3.3%) | 13 (11.8%) | 9 (2.3%) | 0 | 0 | 2 (1.9%) |
| Skin discolouration | 0 | 1 (0.9%) | 1 (0.3%) | 0 | 0 | 0 |
| Skin disorder | 0 | 0 | 0 | 0 | 1 (0.5%) | 0 |
| Skin exfoliation | 0 | 33 (30.0%) | 0 | 12 (8.6%) | 0 | 0 |
| Urticaria | 0 | 0 | 1 (0.3%) | 0 | 0 | 1 (0.9%) |
| Urinary system disorders | | | | | | |
| Urinary tract infection | 0 | 0 | 1 (0.3%) | 0 | 0 | 1 (0.9%) |
| Vascular disorders | | | | | | |
| Flushing | 0 | 0 | 0 | 0 | 0 | 1 (0.9%) |
| Vision disorders | | | | | | |
| Eye pain | 0 | 0 | 1 (0.3%) | 0 | 1 (0.5%) | 0 |

Source: Amendment #007, Table-13

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this page is the manifestation of the electronic signature.**

/s/

Howard Josefberg
7/31/2007 06:48:25 PM
MEDICAL OFFICER

Sharon Hertz
8/6/2007 01:33:56 PM
MEDICAL OFFICER

I concur with the conclusions in this review.

COSULT REVIEW MEMO

DATE: July 27, 2007

TO: Geraldine Smith CDER/DMEP/HFD-510

FROM: Pandu R. Sorey, Ph.D.
Review Scientist, CDRH/ODE/DAGID HFZ-480

THROUGH: Anthony Watson Branch Chief GHDB/DAGID/CDRH/ HFZ-480

SUBMISSION: NDA 22-114 Zingo, Needle-free powder lidocaine monohydrate (LMH) delivery system

APPLICANT / SPONSOR:
Anesiva, Inc., South San Francisco, CA 94080

1.0 INDICATIONS

The sterile LHM (lidocaine hydrochloride monohydrate) product is indicated for use on intact skin to provide local analgesia prior to venipuncture and intravenous cannulation. The sterile 05mg LHM product (— particle size) is contained in a cassette which is a part of the LHM Delivery Device. This device can be used on pediatric subjects (ages 3 to 18 years) prior to a venipuncture and intravenous cannulation with no contraindication other than having intact skin at the site of administration. The final device is a drug/device combination product and must be used by the trained health care professionals licensed to administer human drugs. The LHM Product is supplied sterile, as a single-use disposable device. b(4)

2.0 DEVICE MARKETING HISTORY

This drug/device combination product, the Sterile LHM Product, is not marketed in any country at the time of filing this submission. The proposed auto injector device intended for commercial distribution is model ND5.3A contain sterile LHM, and the device is a ready-to-use, single-use, disposable, needle-free injection delivery system.

3.0 DEVICE DESIGN HISTORY

The system used for the delivery of the lidocaine powder was originally developed in 1996 by PowderJect Technologies, Inc., a subsidiary of PowderJect Pharmaceuticals and originally named the device Dermal PowderJect® (DPJ). The system was developed to deliver dry powdered material through the skin utilizing pressurized helium to accelerate the particles. There were several models of the delivery system and the firm has provided the description of the various models (Table 1, page 4, PMA Device History Report).

The prototype models ND2, ND3, and ND4 were not used in clinical trials. The several versions of the prototype ND5 (ND5.3 and ND5.3A) filled with 0.25 or 0.5 mg lidocaine powder and pressurized with helium gas (20-40 bar) were utilized in Phase 2 and 3 clinical trials listed (Table 2, page 6, PMA Device History Report).

The ND5 is a single-use disposable system is the prototype of the present commercial design and it is comprised of six main components: an aluminum gas micro cylinder, an internal housing, a stainless steel filter, a drug cassette, a nozzle, and a silencer. The gas micro cylinder is filled with helium to a specific pressure and sealed by —
— When the tip of the cylinder is broken the compressed helium gas is released into the downstream section of the device. The ND5.1 device was actuated by pressing the device against the skin and activating the sleeve mechanism, refereed as "sleeve actuation." However, the force needed for the actuation was not acceptable for users, therefore a button actuation was created and used in subsequent versions of the device. The button design is incorporated in the ND5.2 and ND5.3 device models. b(4)

The ND5.3 device (20 bar pressure, 0.5mg drug product) was designed to support clinical trials and was used in one of the pivotal efficacy trials, (3268-2-002-001, US study). This design took into consideration: user experience, user acceptability and feedback, and manufacturing feasibility. It employs the same gas path as the ND5.2 and the device was made less bulky. The button mechanism was further improved and the snap-fit was revised to —
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└ ──┘ Diagrams (provided) identify each component in the device and illustrate the components common to both the ND5.2 and ND5.3 device design.

b(4)

3.1 DESIGN CHANGES:

The device model ND5.3 was modified by implementing five design changes and two materials use changes. The modified device is identified as ND5.3A, and the ND5.3A is to be marketed final device.

3.1.1 Material Changes:

The ND5.3A system includes Drug Cassettes molded from ┌
└ ──┘ Whereas the ND5.3 system included Drug Cassettes molded from ┌
└ ──┘

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3.1.2 Pressure:

The ND5.3 system was configured with nominal 20 bar helium microcylinders manufactured at pilot scale using a semiautomated process. These cylinders were accepted by AlgoRx to a pressure specification of 20.0 bar ±5% (gauge pressure). The ND5.3A system is configured with nominal 21.0 bar cylinders manufactured at ┌
└ ──┘ These microcylinders are accepted by AlgoRx to a pressure specification of 21.0 bar ±1.0 bar (gauge pressure). AlgoRx has conducted testing to compare the in vitro performance of the ND5.3A system with that of the ND5.3 system (Device Comparability Report and PMA section 6.1.8).

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3.1.3 System Design Changes in ND5.3A

The ND5.3A system design includes five modifications to the ND5.3 device:
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└ ──┘

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The final configuration, ND5.3A, is the commercial design that is utilized in the Sterile LHM Product (injector). The ND5.3 and ND5.3A designs were utilized in the clinical trials that support the integrated safety and efficacy of the Sterile LHM Product. Additional in vitro and nonclinical testing was performed, as appropriate, to develop a device that took into consideration user acceptability, clinical trial experience, manufacturing ability, and device performance reliability.

4.0 DEVICE DESCRIPTION

The Sterile LHM Product is a ready-to-use, single-use, disposable, needle-free injection delivery system. Each device is packaged in an individual foil/clear pouch and then packaged into individual bubble-wrap pouches. Twelve pouches are packaged into a labeled carton.

The Sterile LHM device consists of the following major components: Button, Cover, Silencer Cover, Housing, Retainer Clip (two total), Compliant Ball Spacer, Expansion Chamber, Nozzle, Cassette Assembly containing 0.5 mg LHM (Sized Powder), Filter, Silencer Foam, Spring, Helium gas cylinder (pressurized at 21 bar \pm 1 bar). The diagrams of the device components are presented in Figure 1 and Figure 2 (Pgs. 1 and 2, PMA 4.0) depicts the location of the components and the assembled ready to use device.

4.1 Mechanism of Delivery:

This drug/device combination product delivers LHM powder through the skin utilizing pressurized helium to accelerate the drug particles and then deposit in the human tissue. The design of the device includes a safety interlock that prevents the device from being inadvertently actuated prior to appropriate device placement. The powder is administered by first placing the device nozzle end against the site (skin) and pressing it down to release the safety interlock. With the interlock released, the button is then depressed to actuate the device. The device is actuated by depressing (manual activation) of the button that breaks the tip of a micro-cylinder causing the helium gas to flow into the housing. As the gas pressure increases within the housing, the drug cassette (containing 0.5 mg sized powder) film ruptures and the gas expands through the cassette and nozzle, entraining and accelerating the

LHM powder particles. The momentum of the powder particles carries them out of the nozzle and into the skin, whereas the gas flows out of the nozzle, through the silencer and exhausts from the bottom of the cover. Data was collected in the Design Verification studies (PMA section 4.5.1.6) and from ND5.3A lots manufactured that indicated consistent emitted dose as referenced (m3.2.P.5.4, Batch Analyses).

4.2 Device Components and Function:

The Sterile LHM product is a single use disposable drug device combination comprised of components listed in Table below.

Sterile LHM Product Components

| LHM Device Components | Function |
|---|----------|
| Button | |
| Cover | |
| Silencer Cover | |
| Housing | |
| Retainer Clip (two total) | |
| Compliant Ball Spacer | |
| Expansion Chamber | |
| Nozzle | |
| Cassette Assembly-includes film, molded male and female cassette bodies | |
| Filter | |
| Silencer Foam | |
| Spring | |
| Helium Micro-cylinder | |

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4.3 Device Components Compatibility:

The LHM Filled Cassette, the drug product, contains only LHM Sized Powder, therefore the compatibility studies focused on the potential leachables from the sealed cassette halves that constitute the drug product container. The

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┌ The release and stability data show that the LHM Filled Cassettes and Sterile LHM Product show that levels of LHM degradation product are low and do not significantly increase over time. This data supports that there is no apparent chemical reaction to generate detectable degradation products from any interactions between the LHM Sized Powder and the sealed cassettes. The extractable studies found that under normal storage conditions and use of the Sterile LHM Product, the container is compatible with the drug product (m3.2.p.2.6).

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4.2 Device Specification:

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5.0 DEVICE MANUFACTURING, MANUFACTURING FACILITIES:

5.1 Drug Substance Manufacturing Facilities:

The lidocaine hydrochloride monohydrate (LHM), USP, Anesiva, Inc. product code 32-0001, used for the manufacture of the LHM Sized Powder is synthesized in conformance with GMP regulations for Anesiva, Inc. by

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┌ The LHM Sized Powder, used for the manufacture of the drug product (LHM Filled Cassette), is manufactured in conformance with GMP regulations for Anesiva, Inc. by

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5.2 Drug Product Manufacturing Facilities:

Each LHM Filled Cassette, drug product, consists of

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The LHM Filled Cassette (Part No. 31-0037) is manufactured, tested, bulk packed, and shipped in conformance with GMP regulations for Anesiva, Inc. by [redacted] from the following three [redacted]

The final device is assembled and packaged by The Tech Group, Tempe Arizona 85281 and [redacted]

5.3 Microbiological Attributes:

The microbial levels are monitored through the manufacturing process from the unfinished drug substance through the Sterile LHM Product. The LHM powder contained in the sterile LHM device Product is single use and therefore does not contain any preservatives. The unfinished drug substance, lidocaine hydrochloride monohydrate (LHM), USP is tested for microbial limits and bacterial endotoxin (LAL) by the vendor, [redacted] performs the total aerobic microbial count and the total molds and yeasts test with the acceptance criteria of [redacted]. The bacterial endotoxin limit is maximum [redacted]. The test results of six LHM filled cassettes indicate the results were [redacted].

The primary packaging for the Sterile LHM Product is a sealed pouch, and following pouching but prior to [redacted]

6.0 STABILITY:

The stability studies of both the drug product, lidocaine hydrochloride monohydrate (LHM), Filled Cassette, and the final product, sterile LHM Product (autoinjector) are described in this submission (m3.2.p.8). The LHM filled [redacted] condition for the Sterile LHM Product is controlled room temperature. The outline of the stability information is presented in this submission is listed in the table below.

| CTD Section | CTD Section Title | Sub-heading | Contents |
|-------------|---|---|--|
| 3.2.P.8 | Stability [Drug Product, LHM Filled Cassettes and Final Product, Sterile LHM Product] | Not applicable | Description of drug product and device. Stability section organization. |
| 3.2.P.8.1 | Stability Summaries and Conclusion | LHM Filled Cassettes (Drug Product) Stability Summary | Summary of LHM Filled Cassette lots tested, storage conditions used, test methods and acceptance criteria, test schedule, data available, summary of the data analysis, conclusion, and proposed shelf life. |
| | | Sterile LHM Product (Final Product) Stability Summary | Summary of Sterile LHM Product lots tested, storage conditions used, test methods and acceptance criteria, test schedule, data available, summary of the data analysis, conclusion, and proposed shelf life. |
| 3.2.P.8.2 | Post-approval Stability Commitment | LHM Filled Cassettes (Drug Product) | Post-approval commitment and long term stability protocol |
| | | Sterile LHM Product (Final Product) | Post-approval commitment and long term stability protocol |
| 3.2.P.8.3 | Stability Data | Stability Studies (LHM Filled Cassettes) | Retest Data and Accelerated Stability Data |
| | | Formal Stability Studies (Sterile LHM Product) | Data Tables for Primary Stability Lots (long term, intermediate, accelerated, and lot temperature studies) |
| | | Supporting Stability Studies (Sterile LHM Product) | Data tables for clinical lot long term stability studies |
| | | Compiled Sterile LHM Product Data by Method | Combined Lot Data for Assay, LHM Degradation Products, Emitted Dose, and Water Content |
| | | Stress Studies | Summary of Stress Study Conditions Evaluated |

Sterile LHM Product (Final Product) Stability Summary

The primary stability lots of Sterile LHM Product (ND5.3A) were placed on a formal stability study with storage conditions that included the long term room temperature storage condition of $25^{\circ}\text{C} \pm 2^{\circ}\text{C} / 60\% \text{RH} \pm 5\% \text{RH}$, the intermediate condition of $30^{\circ}\text{C} \pm 2^{\circ}\text{C} / 65\% \text{RH} \pm 5\% \text{RH}$, at the accelerated condition of $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \text{RH} \pm 5\% \text{RH}$, and at the low temperature conditions of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ and $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$.

The Phase 3 clinical lot (ND5.3A) stability study was performed to support long term storage at room temperature conditions of $25^{\circ}\text{C} \pm 2^{\circ}\text{C} / 60\% \text{RH} \pm 5\% \text{RH}$. The early Phase clinical lot and development lots (ND5.3) used to support stability were stored at $25^{\circ}\text{C} \pm 2^{\circ}\text{C} / 60\% \text{RH} \pm 5\% \text{RH}$, the intermediate condition of $30^{\circ}\text{C} \pm 2^{\circ}\text{C} / 65\% \text{RH} \pm 5\% \text{RH}$, and at the accelerated conditions of $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \text{RH} \pm 5\% \text{RH}$.

The test methods and stability acceptance criteria used in the stability studies of the primary stability lots of sterile LHM product are listed below.

| Test Method | Acceptance Criteria |
|---|---------------------|
| Appearance of pouch | |
| Appearance of enclosed cassettes and powder | |
| Pouch seal integrity | |
| Water (Moisture) Content by Karl Fischer | |
| Image Analysis (Microscopy) | |
| Particle Size Distribution (PSD3603) | |
| Assay by RT-HPLC | |
| Related Product/LHM Degradation Products by RP-HPLC | |
| Ermitted Dose | |
| Micro cylinder Pressure | |
| Endotoxin | |
| Sterility | |
| | |

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7.0 MANUFACTURING, FACILITIES, AND QUALITY CONTROL

7.1 Design Control Information

Information in this section is presented in accordance with the Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff, issued 3 February 2003. The design control information is included in PMA 4.5.

7.1.1 Design Controls, General Information

The system used for the delivery of the lidocaine powder was originally developed in 1996 by PowderJect Technologies, Inc. (subsequently, acquired by AlgoRx). The system was developed to deliver fine dry powder material through the skin utilizing pressurized helium to accelerate the particles. The ND 5.3 and ND5.3A, comparable device models, were used in Phase 2 and Phase 3 clinical trials, respectively, which were sponsored by AlgoRx. These trials supported the integrated safety and efficacy of the Sterile LHM Product. Additional in vitro and nonclinical testing was performed, as appropriate, to develop a device that took into consideration user acceptability, clinical trial experience, manufacturability, and device performance reliability.

In December 2005, Corgentech Inc. merged with AlgoRx and took over the responsibility of design control for the final configuration, ND5.3A, which is the commercial design that will be utilized in the Sterile LHM Product. In June 2006, Corgentech, Inc. changed its name to Anesiva, Inc.

The three main steps in the Anesiva, Inc. Design Control Process are:

1. Planning, 2. Manage and Monitor Design/Test, 3. Design Transfer to the Manufacturer

Development Life Cycle Phases which include: Device Project Planning, Product Definition (Design Input), Product Design (Design Output), Design Verification, Product Validation (Design Validation) and Design Transfer

For the Sterile LHM Product, activities in several development phases of the plan were conducted by contract organizations. Anesiva, Inc. remains the design authority; however, contract testing facilities were employed for GLP and GMP testing as part of design verification and validation. In addition, the device manufacturing in support of design verification and validation, including the assembly and packaging of the device, was performed by a contract manufacturing organization for Anesiva, Inc.

7.1.2 Design and Development Planning

According to Anesiva, Inc. SOP 02-0200, Design Controls Process, a Device Project Plan for the Sterile LHM Product, ND5.3A device configuration, was created and approved. This plan covers all aspects of device project planning, including required design activities, documentation and approvals, assigned responsibilities, timing, and departmental interfaces.

The Device Project Plan for the Sterile LHM Product (3268 ND5.3A Device Project Plan) and SOP 02-0200, Design Controls Process describes and assigns responsibility for all design control activities including:

- Device project planning (ie, establishment of the project team, project planning);
- Design inputs (ie, defining regulatory strategy, defining user and patient requirements, contractor design planning, DHF establishment, Product Requirements Document completion, projected market forecast, contractor production forecast, projected testing forecast, patent/trademark search, Technical Design Reviews, phase review audit, etc);
- Design output (ie, specification development, external standards assessment, environmental and human factors assessment, risk management and analysis, instructions for use and labeling development, material biocompatibility, supplier identification and evaluation, manufacturing and quality planning, etc);
- Design verification (ie, Design Verification Test Plan(s), Design Verification builds, and test protocols and reports, updates to Risk Management activities/documents, Technical Design Reviews, etc);
- Design validation (ie, Design Validation Test Plan(s), builds, protocols and reports, User Study, Human Factors, Clinical Studies, sterilization and stability testing, Technical Design Reviews, etc);
- Design transfer (ie, process validation, sterilization validation, device manufacturing documentation (DMR), quality inspection, packaging and labeling specifications, Technical Design Reviews, etc); and
- Formal and informal design reviews, risk assessments and audits at appropriate intervals throughout the course of the project plan.

Risk Management assessment and risk control activities are summarized in the LHM Device Risk Management Plan and Summary Report. This summary identifies, quantifies and assesses control of potential risks related to the use of the Sterile LHM Product. The process of assessing risk, rating severity and occurrence, analyzing ways to mitigate and manage risk to the benefit of the user, and reporting the risk management plan is described in Anesiva, Inc. SOP 02-0203, Risk Management. As per Anesiva's design controls process, the risk management plan is updated periodically throughout the development effort to reflect new information concerning risk and/or effectiveness of mitigations.

7.1.2.1 Design Input:

Design Inputs are outlined in the Device Project Plan per SOP 02-0200, Design Controls Process. The primary design input requirements are established in the formal Product Requirements Document per Anesiva, Inc. SOP 02-0202, Device Product Specification Development. The Product Requirements Document addresses the intended use of the device, as well as the needs of the user and patient. It includes a functional description, intended use, regulatory requirements, user interface requirements, safety requirements, physical characteristics, performance specification, packaging and labeling requirements, manufacturing requirements, and storage/stability requirements.

The sterile device requirements document includes both the user requirements and the product requirements for the sterile LHM device. Additional design inputs included a device testing forecast, projected market forecast, and patent trademark review. Design inputs listed in the Anesiva, Inc. Product Requirements Document were refined based on the risk assessment experiences from two Phase 3 clinical trials (Summary, PMA Section 6.2).

The Sterile LHM device is designed for a pediatric patient population, aged 3 to 18 years. The anticipated users of the device are healthcare professionals licensed to administer topical local anesthetics to patients. The Sterile LHM Product is a single use device, supplied sterile.

7.1.2.2 Design Output:

Requirements and criteria for design outputs are based on the Product Requirements Document. Formal approved specifications and drawings are established for each component as well as for the assembled device, packaged and labeled device and final sterile device (Sterile LHM Product) (Specifications, m3.2.P.5.6). The specifications are a part of the Device Master Record created by the contract manufacturer and approved by Anesiva, Inc.

Essential outputs were identified based on the Risk Management Assessment which includes a plan for risk resolution and mitigation (Risk Management Plan). Specific component requirements, manufacturing controls, in-process testing, final acceptance tests and supplier controls have been established for the essential outputs and are included in the Device Master Record as part of the Design Transfer process. The essential are summarized in the table below.

**Appears This Way
On Original**

| Item | Critical Features/Characteristics | Controls |
|---|-----------------------------------|----------|
| Housing | | |
| Helium Micro cylinder | | |
| Filter | | |
| LHM Filled Cassette (Drug container- closure) | | |
| Nozzle | | |
| Retainer | | |
| Silencer Cover | | |
| Spring | | |
| Cover | | |

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Table continued

| Item | Critical Features/Characteristics | Controls |
|--------|-----------------------------------|----------|
| | | |
| Button | | |
| Label | | |
| Pouch | | |

b(4)

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7.1.2.3 Design Review:

Design Reviews are performed throughout the Anesiva, Inc. Development Life Cycle Phases. Anesiva SOP 02-0200 Design Controls Process stipulates at what Development Life Cycle Phase design reviews must be conducted; SOP 02-0205 Technical Design Review prescribes how reviews will be conducted. Technical Design Review, describes the formal procedure for performing design review during device design and development. A Technical Design Review is a documented, comprehensive, systematic examination of the design to evaluate the adequacy of the design requirements (ie, Product Requirements), evaluate capability of the design to meet these requirements, and to identify problems.

7.1.2.4 Design Verification:

Design verification of the ND5.3A configuration was conducted in accordance with the Anesiva SOP 02-0201, Design Verification and Design Validation Protocols and Reports. A Design Verification Plan was developed and approved that describes in detail the verification activities that support the development of the Sterile LHM Product. This plan highlights the essential tests, analysis, and acceptance criteria that demonstrate the device safety and effectiveness based on the ability of the design output to meet design input requirements, and successful implementation of risk mitigation measures.

Each design verification test is prescribed by an approved protocol, which stipulates the applicable standards, the test method(s), test article requirements, acceptance criteria, and data collection/reporting requirements. Verification tests use analytical methods that have been validated, as appropriate (section m3.2.P.5.3). After design verification testing is conducted, a test report is prepared and approved, which identifies the test method, tester(s), test date(s), test outcome, and raw data.

The summary table below outlines the sterile LHM Product (device) design verification testing regime.

2 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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7.1.2.5 Design Validation:

The Sterile LHM Product ND5.3A (commercial configuration) has been evaluated in two Phase 3 clinical studies and one Phase 1 clinical study as described (LHM Device Design Validation Plan, Rev. 00). The studies are described in CTD section m5.3. for information on the following studies: Study 3268-3-003-1 US A Phase III, Randomized, Double-Blind, Placebo Controlled Study to Confirm the Effectiveness and Safety of ALGRX 3268 in Pediatric Subjects, Study No. 3268-3-004-1 Phase III, Randomized, Double-Blind, Placebo Controlled Study to Confirm the Effectiveness and Safety of ALGRX 3268 in Pediatric Subjects and Study 3268-1-005-1 An open-label study to determine the sound emission levels produced by ALGRX 3268 ND5.3A, a needle-free injector for use in healthy adult volunteers

In addition to these above studies, there were three additional studies in the pediatric population and one pharmacokinetic study in adults that support the proposed indication for the sterile LHM device that utilized a comparable device configuration (ND5.3). These studies are: ND5.3 Controlled Pediatric Study 3268-4-400-001, Study No. 3268-4-401-001 and Study No. 3268-2-002-1

The Design Validation activities conducted in addition to the clinical studies cited above follow the Anesiva, Inc. SOP 02-0201 Design Verification and Design Validation Protocols and Reports. The Design Validation Plan incorporated the following additional design validation studies:

Validation no. 1, User Study: This study evaluated the usability of the proposed Instructions for Use and the Sterile LHM Product to determine whether typical naïve users are able to understand and use the product given cursory training, the Instructions for Use and opportunity to practice use of the device. The study evaluated the user's ability to properly administer the device after having been exposed to the training and Instructions for Use as documented on a participant questionnaire. The acceptance criteria required — of the participants to correctly answer understandability questions on the administration of the device, and to actuate a test device properly. The training devices and test devices used by the participants were manufactured and assembled in the same manner as the commercial production devices. The sterile LHM Device user study was successful with 93% of the participants correctly answering the understandability questions correctly and 100% of the participants actuating the device correctly.

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Validation no. 2, Human Factors Independent Evaluation: An independent assessment of the human factors embodied in the ND 5.3A commercial design was provided by an industry expert. A Certified Professional Ergonomist was hired to evaluate the device from the viewpoint of an expert working and teaching medical product design. The details of test protocol is provided in PMA 4.5.1.7, pg. 3. and overall the device design was found to be acceptable to the users.

7.1.2.6 Design Transfer:

The design transfer process is addressed in Anesiva, Inc. SOP 02-0200, Design Controls Process. The design transfer activities and responsibilities for the sterile LHM device are outlined in the Device Project Plan. A specific Sterile LHM Product Design and Technology Transfer Plan, 77-0001 has been developed to outline the plans and requirements of the transfer of the manufacturing to The Tech Group, Anesiva's contract manufacturer for the LHM Product (pre-sterilization) and address the scale up plans from clinical/pilot scale to commercial

manufacturing for the device. In addition, The Tech Group follows SOP TEM00017 to manage process validation at its manufacturing facility.

The requirements for the Device Master Record (DMR) are outlined in Anesiva, Inc. SOP 02-0304, Device Master Record. The DMR includes device specifications, production and process specifications (The Tech Group operations), sterilization process specifications, packaging and labeling specifications, and quality assurance specifications (conducted at various contract sites and at Anesiva, Inc.). The DMR is created by Anesiva, Inc. (device specifications), various contract manufacturers (The Tech Group, ——— and contract test facilities. Anesiva, Inc. approves the product specific aspects of the DMR, and requires change of notification/approval as part of its Quality Agreements with key contract manufacturers and test laboratories. The detailed information related to the Design Transfer is provided in PMA 4.5.1.8.

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7.1.2.7 Design Changes:

Changes made during the design cycle are documented, assessed, and approved per Anesiva SOP 02-0200. The procedure provides a process for making design change requests, assessing and approving plans for changes, verifying or validating changes, tracking of all required activities, and eventually filing a design change record in the design history file. The SOP includes a planning guideline for design changes to support thorough consideration of appropriate design activities based on the type of change.

Post design transfer changes for routine production are governed by the Anesiva, Inc. SOP 02-0301, Change Control Process. Each change, whether initiated by Anesiva, Inc. or the contract manufacturer, requires the assessment by an Anesiva, Inc. Change Review Board (CRB). The detailed information related to the Design Changes is provided in PMA 4.5.1.9.

7.1.2.8 Design History File:

Anesiva Inc. SOP 02-0204, Design History File (DHF) establishes a standard system for documenting the development history of a new device or a modification of an existing design. The DHF for the ND5.3A Sterile LHM device (to be marketed) product design follows the outline of the Anesiva, Inc. Device Project Plan that was approved in February 2006. It contains sections for all key phases of design control, such as Device Project Planning, Product Definition (Design Input), Product Design (Design Output), Design Verification, Product validation, risk management activities, design reviews and Design Transfer. The detailed information related to the Design History is provided in PMA 4.5.1.10.

7.2 Manufacturing Information:

7.2.1 Quality System Procedures:

At Anesiva the guiding document in the quality system is the Quality Manual, SOP 01-0001. The remaining documents in the system are separated into operational sections and then further broken down into specific document types by functional area such as: policies and procedures, methods, specifications, protocols, and reports. SOP 01-0001, Quality Manual, contains Anesiva, Inc. corporate policy and philosophy for the quality operating system, which it terms the "GMP operating system". ("quality system"). The Quality Manual defines the overall structure of the quality system and establishes the corporate responsibilities and expectation for quality and compliance. The detailed information related to the Quality System at Anesiva is provided in PMA 4.5.2.1.1.

The Tech Group is the FDA-registered contract manufacturer responsible for the manufacturing, assembly, and packaging of the Sterile LHM Product. As a medical device manufacturer, The Tech Group maintains its own Quality Manual, TEM-QMP00001. The Tech Group Quality Manual incorporates references to ISO 13485 and FDA 21 CFR Part 820. It covers the general requirements of The Tech Group's Quality Management System, documentation requirements, management responsibility, management review, resource management, process controls, measurement, and analysis and improvement. The Tech Group has its own document control system and structure of documents which include the Device Master Record, Work Procedures and Device History Records used in the manufacture of the sterile LHM device. The detailed information related to the Quality System at Tech Group is provided in PMA 4.5.2.1.1.

7.2.2 Use of Standards:

The national and internationally recognized standards employed by Anesiva, Inc. during the design, verification testing, validation, and manufacturing of the sterile LHM device are listed in table below.

Device Standards List Applicable to the Device

| Standards Number | Standards Title |
|-----------------------------|--|
| ANSI/AAMI/ISO 14937: 2000 | Sterilization of health care products — General requirements for characterization of a sterilizing agent and the development, validation, and routine process control of a sterilization process for medical devices |
| ISO 21649: 2006 | Needle-free injectors for medical use-Requirements and Test Methods |
| ANSI HE48-1: 1993 | Human Factors Engineering Guidelines and Preferred Practices for Design of Medical Devices |
| ANSI/AAMI/ISO 14971: 2000 | Medical Devices – Application of Risk Management to Medical Devices |
| USP 29 | The United States Pharmacopoeia 29, Mack Publishing Company |
| ISO/DIS 10993-1: 2003 | Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing |
| ANSI/AAMI/ISO 11137: 2006 | Sterilization of Health Care Products-Requirements for Validation and Routine Control--Radiation Control |
| ANSI/AAMI/ISO 11137-1: 2006 | Sterilization of Medical Devices, Microbiological Methods-Part 1: Estimation of Population of Microorganisms on Products |
| ANSI/AAMI/ISO 11137-2: 2006 | Sterilization of Medical Devices, Microbiological Methods-Part 2: Tests of Sterility Performed in the Validation of a Sterilization Process |
| AAMI TIR 27: 2001 | Sterilization of Health Care Products – Radiation Sterilization Substantiation of 25 kGy as a sterilization—Method VDmax |
| ASTM F 1886-98: 2004 | Standard Method for Determining Integrity of Seals for Medical Packages by Visual Inspection |
| ASTM F88-06 | Standard Test Method for Seal Strength of Flexible Barrier Materials |
| ASTM F 2096-04 | Standard Test Method for Detecting Gross Leaks in Medical Packaging by Internal Pressurization (Bubble Test) |
| ASTM D 4332-01 | Standard Practice for Conditioning Containers, Packages or Packaging Components for Testing |
| ASTM D 4169-05 | Standard Practice for Performance Testing of Shipping Containers and Systems |
| ASTM F 1980: 2002 | Standard Guide for Accelerated Aging of Sterile Medical Device Packages |
| AAMI TIR 29: 2002 | Guide for Process Control in Radiation Sterilization |

7.2.3 Purchasing Controls:

The information related to the potential contract organization, vendors, suppliers and contractors and consultants for Anesiva, Inc. are selected according to SOP 02-0404. The components and raw materials used in manufacturing at The Tech Group are to comply with Anesiva, Inc., specifications and meet The Tech Group SOP, TEM-SOP00010. The detailed information related to the Purchasing Controls are provided in PMA 4.5.2.4

7.2.4 Production and Process Controls:

Anesiva, Inc. does not manufacture clinical or commercial products. The Tech Group is Anesiva Inc. 's contract manufacturer for the sterile LHM device. — is Anesiva, Inc. 's contract sterilizer.

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The Tech Group is responsible for the manufacture of the molded components used in the sterile LHM device. The Tech Group assembles all parts of the device and performs the final labeling, pouching, seal, and packaging of the device. This production at The Tech Group is performed according to the Device Master Record. Anesiva, Inc. approves all revision and changes to the Device Master Record. All device assembly is performed in an ISO Class 8 environment.

The sterilization of finished packaged product is performed by _____ Product
is transported to and from _____ under controlled temperatures. _____

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_____ Validation of the sterilization

process is discussed in PMA 4.5.2.7.

The detailed information related to the Production and Process Controls is provided in PMA 4.5.2.5

7.2.5 Inspection, Measuring and Test Equipment:

Equipment and tools used at Anesiva, Inc. in the design, inspection, and testing of raw materials, intermediates, devices, and finished product are calibrated and maintained per SOP 02-0800, inspection/test activities are described in more detail in sections 4.5.2.9 and 4.5.2.10. Equipment owned by contract manufacturers or contract laboratories is calibrated and maintained according to their own quality system.

For the manufacture, assembly, and packaging of the Sterile LHM Product occurring at The Tech Group, TEM-SOP00036, Inspection, Measuring, and Test Equipment Calibration is followed. The detailed information related to the Inspection is provided in PMA 4.5.2.6.

7.2.6 Process Validation (Master Plan):

The Anesiva, Inc. document 72-0001, Process Validation Master Plan-Sterile LHM Device, provides an overview and description of all the manufacturing processes that have been validated for the device. It outlines key process validation acceptance criteria and includes references to the LHM Device Risk Management Plan. The Risk Management Plan and Summary Report were created per Anesiva, Inc. SOP 02-0203, Risk Management. It evaluated potential risks to the device and drug product.

Critical manufacturing process steps have been validated and each is documented in a separate validation plan.

The major processing steps include:

1. Assembly of the device (including placement of the LHM Sized Powder filled cassettes into the device).
The validation of the manual assembly process consisted of three manufacturing lots produced in accordance with a Performance Qualification (PQ) Protocol.
2. Primary and secondary packaging of the device. The validation of the primary and secondary packaging process consisted of three manufacturing lots, packaged in accordance with a Performance Qualification (PQ) Protocol. The packaging process follows the device manual assembly process and produces a package ready for sterilization and subsequent commercial distribution.

3. _____

_____ including bioburden determination, minimum dose verification, dose mapping of the production

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irradiator, and maximum dose assessment of degradation of the LHM Filled Cassette, device and package integrity.

4. Shipping and handling. Validation for shipping and handling includes simulated distribution studies per ASTM 4169 utilizing packaged, sterilized and aged devices, as part of the design verification testing. Inspection, package integrity, and functional testing were included in the studies.
5. Overall process qualification. A minimum of three process qualification lots have been manufactured using the commercial GMP manufacturing process. The data from the manufacturing and testing of three lots of devices was assessed and it met the requirements specified in the validation plans. The overall acceptance criteria for the manufacturing of three lots of devices (manually filled, assembled, packaged, sterilized, shipped) took into account in-process testing and inspection, batch record requirements, and Certificate of Analysis specifications. Batch record is provided.

There is no software in the device itself, or used in the process of manufacturing the device. The detailed information related to the Production and Process Controls are provided in PMA 4.5.2.7

7.2.6 Process Validation (Validation Procedures):

Anesiva, Inc.- The required elements and documentation for general process validation are outlined in SOP 02-0613, Process Validation. This SOP covers processes used in the manufacture of devices, drug, and/or drug/device combination products. The specific standards, methods, and procedures used to conduct sterilization validations are described in SOP 02-0725, Sterilization Validation. This SOP applies to all products terminally sterilized and labeled as "sterile."

At the Tech Group device process validation plans for the manufacture, assembly, and packaging of the device were written and executed by The Tech Group, according to TEM-SOP00017, Validation Master Plan Criteria.

The description of the individual validation plans, manufacturing site validation plan and the acceptance criteria are provided in PMA 4.5.2.8, pages 3-4.

7.2.7 Final Acceptance Activities:

All products for GMP use must be dispositioned by Anesiva, Inc. Quality Assurance group which designate the specific use allowed for a drug substance, drug product, component, or device. Per SOP 02-0900, Lot Release and Product Disposition one of the following status categories will be used for disposition:

Quarantine: Lot is not available for use and requires further evaluation by Quality Assurance prior to use.

Rejected: Lot is not available for further processing or distribution to market or clinic.

Acceptable for Further Processing: Lot is made available for further processing to the next applicable manufacturing step, but the lot is not released for distribution.

Released: Lot is acceptable for use in a further manufacturing step, distribution to market or clinical for human use and does not require any further evaluation by quality Assurance.

The detailed description and criteria to evaluate the device Final Acceptance is provided in PMA section 4.5.2.10.

8.0 NON-CLINICAL STUDIES:

8.1 Toxicological Studies

Results and summaries of toxicology studies conducted with the sterile LHM device are presented in the CTD Nonclinical Module 2, section 2.6.6 and section 2.6.7. Additional information is included in PMA section 3.5.1 regarding the summary tables of all nonclinical studies conducted to support the proposed indication for the LHM device.

8.2 Biocompatibility Studies:

In accordance with the LHM Device Material Biocompatibility Assessment, Rev 00, and Anesiva SOP No. 02-0726, Biocompatibility Safety Testing, the Sterile LHM device was tested to establish the biocompatibility of LHM human-contact materials (cover, silencer cover, actuation button, washer, film, and nozzle). b(4)

The device was tested in accordance with ISO 10993-1:2003, Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing, and FDA/CDRH Blue Book Memo no. G95-1, the sterile LHM device was assessed for body contact type and duration. The contact type is based on the indications and labeling for the product, which is for the administration of needle-free injections to intact skin on the back of hand or antecubital fossa. The duration is based on the intended use, which is as a single use product, and therefore, under 24 hours. Thus, the Sterile LHM Product body contact type is Surface/Skin contact of Limited duration. Based on this classification, the required test regime is Cytotoxicity, Sensitization, and Irritation or Intracutaneous Reactivity.

Recent biocompatibility testing performed relates specifically to the commercial sterile LHM device design, and supports previous testing performed in earlier clinical development. The commercial configuration of this device uses the same materials of construction as the clinical configuration. The only changes in the commercial configuration that might affect biocompatibility relate to color tints in three molded components.

The biocompatibility test articles were manufactured and sterilized in the same manner as the commercial devices will be; details concerning these test samples are documented and stored in the Sterile LHM Product Design History File. The test protocols were all pre-approved, and testing was performed under GLP conditions at _____ or under _____ sponsorship.² All of the tests passed; commercial device components are biocompatible. Test details for the Cover, Silencer Cover, and Button tests are provided in table below. b(4)

| Test Name | Test Description | Test Article and Results/ Report No. |
|---------------------------|--|---|
| Cytotoxicity | ISO 10993-5: In Vitro Cytotoxicity (L-929) | Cover: Pass (Non cytotoxic)/ 327067 Silencer Cover: Pass (Non cytotoxic)/ 327838 Button: Pass (Non cytotoxic)/ 327060 Washer: Pass (Non cytotoxic)/ v0014-130- film: Pass (Non cytotoxic)/ v0014-130-10; Nozzle: Pass (Non cytotoxic)/ v0014-130- b(4) |
| Sensitization | ISO 10993-10: Sensitization (Magnusson Kligman Maximization – saline and cottonseed oil, guinea pig) | Cover: Pass (Nonsensitizing)/ 43837 Silencer Cover: Pass (Nonsensitizing)/ 44187 Button: Pass (Nonsensitizing)/ 43839 Washer: Pass (Nonsensitizing)/ t1261-300-301- film: Pass (Nonsensitizing)/ t1261-300-t1261-301-10 Nozzle: Pass (Nonsensitizing)/ t1261-300-301- b(4) |
| Intracutaneous Reactivity | ISO 10993-10: Irritation (Injection – saline and cottonseed oil, rabbit) | Cover: Pass (Nonirritating)/ 43838 Silencer Cover: Pass (Nonirritating)/ 44188 Button: Pass (Nonirritating)/ 43840 Washer: Pass (Nonirritating)/ t1251-800- film: Pass (Nonirritating)/ t1251-800-10 Nozzle: Pass (Nonirritating)/ t1251-800- b(4) |
| Acute Systemic Toxicity | ISO 10993-11: Systemic Toxicity (Saline and cottonseed oil, mouse) | Washer: Pass (Nontoxic)/ t1264-500- film: Pass (Nontoxic)/ t1264-500-10, b(4) |

| | | | |
|--------------|--|--|------|
| Genotoxicity | ISO 10993-3: Genotoxicity (Bacterial Reverse Mutation – saline) | Washer: Pass (Nonmutagenic)/ v0023-211-212- film: Pass (Nonmutagenic)/ v0023-211-10- | b(4) |
| | ISO 10993-3: Genotoxicity (Bacterial Reverse Mutation – DMSO) | Washer: Pass (Nonmutagenic)/ v0023-211-212- film: Pass (Nonmutagenic)/ v0023-212-10- | b(4) |
| | ISO 10993-3: Genotoxicity (Mouse Bone Marrow Micronucleus – saline) | Washer: Pass (Nongenotoxic)/ t0212-500- film: Pass (Nongenotoxic)/ t0212-500-10- | b(4) |
| | In Vitro Chromosomal Aberration in Mammalian Cells | Washer: Pass (Nongenotoxic)/ v0002-130- film: Pass (Nongenotoxic)/ v0002-130-10- | b(4) |
| Implantation | ISO 10993-6: Local Effects after Implantation (14 d, Intramuscular – rabbit) | Washer: Not significant (macroscopic); moderate irritant (microscopic)/ t1250-802-th035-800- film: Pass (Nonsignificant/nonirritant)/ t1250-802-th035-800-10- | b(4) |
| | ISO 10993-6: Local Effects after Implantation (12 wks, Intramuscular – rabbit) | Washer: Not significant (macroscopic); slight irritant (microscopic)/ t1250-812-th035-800- film: Pass [Not significant (macroscopic); nonirritant (microscopic)]/ t1250-812-th035-800-10- | b(4) |

Earlier in clinical development, a series of GLP biocompatibility tests and USP physicochemical tests were conducted to demonstrate that components (likely to come in skin contact with users or patients) of the ND5.3 device (the configuration prior to the commercial configuration) were nontoxic. Tests were conducted on 3 used in the cassette washer (P/N 2003001), the 4 used in the cassette film (P/N 6010001), and 5 used in several device components and represented by the device nozzle (P/N 2100001). Comparability of the ND5.3 and ND5.3A device design configurations is discussed in the ND5.3/ND5.3A Device Comparability Report. The ND5.3 biocompatibility testing was conducted in accordance with ISO 10993-1 and the Cytotoxicity, Sensitization, and Irritation/Intracutaneous Reactivity finished clinical ND5.3 device configuration were conducted by under GLP controls.

8.3 Stress Studies:

As part of the LHM Design Verification program, various bench tests have been performed to evaluate device performance when subjected to a variety of stress conditions. The LHM Design Verification Plan defined various tests to be performed, which are designated in the plan. A table listing the verification studies performed and the corresponding acceptance criteria is located in section 4.5.1.6, Design Verification. All stress tests were performed on devices that are representative of the commercial LHM device (ie, same materials of construction and finished device sterilization processing). As a single use device designed for manual, mechanical operation, the most significant stresses that the device will be subjected to are environmental. There is no possibility of reuse due to the device integral, custom filled drug cassette, and the single pressure source from the helium filled cylinder.

A summary of test results is provided in Table below.

Stress Test Summary Results

| Test Focus and Stress Condition(s) | Test Protocol | Result |
|---|---------------------------------|------------|
| Dose accuracy within and outside expected operating temperature range: 15°C, 30°C, 37°C | Verification no. 5 | Acceptable |
| Dose penetration within and outside expected operating temperature range: 5°C, 15°C, 30°C, 37°C | Verification no. 6 | Acceptable |
| Dose accuracy at barometric pressure equivalent to 7000 ft | Verification no. 7 | Acceptable |
| Dose penetration at barometric pressure equivalent to 7000 ft | Verification no. 8 | Acceptable |
| Sterile barrier and product performance after exposure to simulated distribution cycle under a variety of typical and high temperature climate conditions | Verifications no. 18 and no. 20 | Acceptable |
| Sterile barrier and product performance after exposure to barometric pressure equivalent to typical commercial air freight conditions | Verification no. 19 | Pending |

8.4 Wear Studies:

As a single use device with no possibility of reuse due to the integral, custom drug cassette, and single-use helium cylinder, the Sterile LHM Product is not subject to wear and has not been tested for this condition. Actuation Verification Reliability was to simulate user experience in operating the device to establish reliability. Device actuation was verified in this test to establish reliability at a 95% confidence level with 99% reliability independent of lot size. There were no device failures in the test and the results verify an out of box failure rate of less than 1%.

8.5 Shelf life Studies:

Verification tests are being performed to confirm the ability of the sterile LHM device to maintain product functionality and sterile barrier protection after a simulated distribution environment and storage under real time and accelerated aging conditions. The verification tests are part of the LHM Device Design Verification Plan, Rev.01. The objective of these studies is to establish and confirm product conformance to specification over a shelf life of at least two years.

Devices will be tested for Real Time and Accelerated Aging at various time points to establish packaging and product performance per ASTM F1980, Standard Guide for Accelerated Aging of Sterile Medical Device Packages. ASTM standard D4332, Standard Practice for Conditioning Containers, Packages or Packing Components for Testing and D4169, Standard Practice for Performance Testing of Shipping Containers and Systems will be used in the study. The sterile barrier will be tested based on a bubble test and on a tensile pull test of a subset of the package samples per ASTM F2096, Standard Test Method for Detecting Gross Leaks in Medical Packaging by Internal Pressurization (Bubble Test) and F88, Test Method for Seal Strength of Flexible Barrier Materials.

The product will be evaluated based on visual inspection to include examination of packaged and opened devices for package integrity, label integrity/legibility, abrasion, crack, color, and other critical attributes. Device performance will be evaluated by actuating the device, particulate testing, and measuring emitted dose. The testing time points are specified.

COMMENTS/RECOMMENDATIONS:

Considering the information provided in this NDA regarding the design, technological characteristics, safety, manufacturing and performance characteristics, the proposed Zingo autoinjector (device) is safe and effective for use as indicated.

Pandu R. Soprey July 30, 07

Pandu R. Soprey, Ph D
Review Scientist, CDRH/ODE/DAGID HFZ-480

Anthony Watson 8/3/07

Anthony Watson
Anthony D. Watson, BS, MS, MBA
Chief, General Hospital Devices Branch, HFZ-480
Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices
Center for Devices and Radiological Health, U.S. Food and Drug Administration

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/s/

Geraldine Smith
8/6/2007 08:43:20 AM
CSO

STUDY ENDPOINT REVIEW

| | |
|-------------------------------|---|
| SEALD ACTION TRACK NUMBER | 2007.002.A.00032 |
| APPLICATION NUMBER | NDA 22-114 |
| LETTER DATE/SUBMISSION NUMBER | November 21, 2006 |
| DATE OF CONSULT REQUEST | March 29, 2007 |
| REVIEW DIVISION | Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) |
| MEDICAL REVIEWER | Howard Josefberg |
| REVIEW DIVISION PM | Geri Smith |
| SEALD REVIEWER(S) | Ann Marie Trentacosti |
| REVIEW COMPLETION DATE | April 25, 2007 |
| ESTABLISHED NAME | Zingo |
| TRADE NAME | Lidocaine Hydrochloride Monohydrate Needle-Free Powder Delivery System |
| APPLICANT | Anesiva |
| ENDPOINT(S) CONCEPT(S) | Pain assessment |
| INSTRUMENT(S) | Wong-Baker FACES Pain Rating Scale with Modified Instructions |
| INDICATION | Provide local analgesia prior to venipuncture or intravenous cannulation |
| INTENDED POPULATION(S) | Patients \geq 3 -years of age receiving venipuncture or intravenous cannulation |

1 EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) regarding NDA 22-114. The consultation requested SEALD assess the acceptability of the primary efficacy endpoint using a modified version of the Wong-Baker FACES Pain Scale.

The review concludes that the content validity of the modified instructions has not been substantiated in order to determine that the revised instructions are acceptable. The sponsor's justification of the instrument modification is primarily based upon the opinion that children do not pay attention to verbatim verbal instructions and in the establishment of construct validity of the instrument. However, the sponsor has not shown that the new instructions are appropriate and understandable for the target population. Establishing content validity is especially important for the proposed target population of children ages ≥ 3 to 18 year of age in which one set of instructions may not be appropriate for all ages.

In addition, since a modified version of the Wong-Baker FACES scale is utilized in the clinical trials, it is inaccurate for the sponsor to refer to the scale by this name in labeling. If efficacy statements concerning this modified instrument are included in the label, a more generic description (i.e. faces pain scale) should be considered.

2 ENDPOINT REVIEW

2.1 Instruments

See Appendix 4 for a representation of the Wong-Baker FACES Pain Rating Scale, Faces Pain Scale-Revised, and the Wong-Baker FACES Pain Rating Scale with Modified Instructions used in the Zingo pivotal trials.

To assess the effect of Zingo in providing local analgesia prior to venipuncture or intravenous cannulation in patients ≥ 3 years of age in their pivotal trials, the sponsor developed an instrument to evaluate pain intensity which was based upon the combination of two traditional pain scales (Wong-Baker FACES Pain Rating Scale and the Faces Pain Scale-Revised). The revised pain assessment instrument, the Wong-Baker FACES Pain Rating Scale with Modified Instructions, combined the pictures from the Wong-Baker FACES Pain Rating Scale (W-B) and the verbal instructions from the Faces Pain Scale-Revised (FPS-R). The modified instructions were identical to the FPS-R except that "very much pain" from the FPS-R was changed to "a lot of pain" in the modified instrument.

The decision to modify the W-B scale was discussed by DAARP and the sponsor during the pre-NDA meeting on June 19, 2006. The sponsor was informed that they would need to submit an argument that supports applying the instructions from one pain scale to a different pain scale.

The original Wong-Baker FACES scale was developed in the 1980s as a pain assessment tool in children. In a validation study, the instrument was compared to five other pain scales in hospitalized children ages 3 to 18 years. As noted by the author, although the children preferred the W-B scale, none of the six scales demonstrated superiority in validity or reliability.¹

The Faces Pain Scale (FPS) was originally developed in 1990 as a self-report measure used to assess the intensity of children's pain. The Faces Pain Scale-Revised (FPS-R) created a six face scale from the original seven face scale in order to make it compatible in scoring with other self-rating and observational scales which use a common metric (0-5 or 0-10). As noted by author, the FPS-R was validated by correlating the revised instrument with a visual analogue scale (VAS) measure in children aged 5-12 who were rating the intensity of their ear piercing. In another study, strong correlations with VAS and colored analogue scales (CAS) during hospitalization for surgical and non-surgical painful conditions in children 4-12 years of age were observed.²

In their NDA, the sponsor provided the following rationale for the instruction modifications:

- While both scales have six face diagrams that correspond to numerical pain measurements, the instructions for FPS-R are simpler and easier to administer than those for the original Wong-Baker FACES scale.
- The FPS-R instructions directly measure the child's pain by asking the child to "point to the face that shows how much you hurt right now," whereas the Wong-Baker instructions may reflect the child's mood by asking the child to "choose the face that best describes how he/she is feeling."

2.2 Claim Structure

Proposed indication: Zingo is indicated for use on intact skin to provide local analgesia prior to venipuncture or intravenous cannulation in patients ≥ 3 years of age.

2.3 Endpoint Model

To support their proposed indication:

Primary Endpoints:

- Measurements of pain were made immediately following the venous procedure using the Wong-Baker FACES Pain Rating Scale with Modified Instructions pain rating scale in patients 3-18 years of age

Secondary Endpoints:

- A 100 mm subject visual analogue scale (VAS) of pain intensity in patients 8-18 years,
- A 100 mm parent VAS on which the parent assessed their child's pain

2.4 Conceptual Framework

The concept measured is pain intensity.

2.5 Content Validity

In order to justify the content of the modified instrument, the sponsor elicited opinion of [redacted] provided the following points to justify the sponsor's position that the details of the instructions do not make a difference in outcome of pain ratings.:

b(6)

- The most salient target of attention for people making a rating on the W-B is the pictures of faces. These pictures endure while the verbal instructions are transient.
- In transferring the verbatim instructions into gist memory, people translate what they hear into something they can understand and remember. They do not remember verbatim text unless specifically requested and rehearsed. An adult might translate the instructions into a mental model or gist memory of a continuously increasing scale like a ruler or thermometer. A young child would probably not make that translation, because of unfamiliarity with rulers and thermometers.
- The gist of the instructions for the FPS-R and the W-B is identical despite minor differences in wording. In both, the child's attention is drawn to the fact that the left-most picture shows no hurt and the right-most picture shows the most hurt and the intermediate pictures show intermediate (increasing) amounts of hurt.
- In clinical use of faces pain scales, and even in the instructions for research use, there is considerable latitude for the examiner to tailor instructions to the child, allowing the examiner to try to ensure that the child understands the task. For example, the FPS-R instructions specify to use whichever word, hurt or pain seems right for a particular child. Thus minor variations in instructions would be a routine part of use of faces pain scales with children.

Comments: Overall, [redacted] comments are based upon conjecture and not facts. In considering such a broad and developmentally diverse target population of patients ≥ 3 -18 years of age, it cannot be assumed that a 3 year old would understand and interpret instructions on par with an 18 year old. In addition, testing procedures in clinical practice do not necessary reflect the rigorous methodology utilized in clinical trials designed to assess treatment benefit.

b(6)

In summary, the content validity of the Wong-Baker FACES Scale with Modified Instructions has not been determined in order to justify that the new instructions are appropriate and understandable for the target population. Without specific data based upon cognitive debriefings, it cannot be determined to what extent the target population understands and interprets the revised instructions.

2.6 Other Measurement Properties

To validate the Wong-Baker FACES Scale with Modified Instructions, the sponsor performed an internal validation assessment by correlating the Wong-Baker FACES (W-B) scale with

modified instructions with other pain intensity scales (FPS-R and the 100 mm VAS scale) in all controlled pediatric studies. According to the sponsor, there was a strong correlation (correlation coefficient 0.86 by Pearson and 0.84 by Spearman, $p < 0.001$) between the Wong-Baker FACES scale and VAS within 909 subjects. The correlation between the FPS-R scale and VAS within 32 subjects from study 3268-4-401-001 was also strong (correlation coefficient 0.77 by Pearson and 0.70 by Spearman, $p < 0.001$). For children in the 3–7 year old group, only the Wong-Baker FACES or FPS-R were used (due to lack of validation of the VAS in young children); therefore, analysis of the correlation of VAS to either of these FACES scales was not possible for this youngest age group.

In addition to the above, [redacted] provided the sponsor's justification that the revisions of the verbal instructions from the Wong-Baker FACES Pain Rating Scale (W-B) did not result in any significant differences in the interpretation of results in pain assessment. [redacted] provided the following information in the NDA:

b(6)

In a study by Nix, 148 children ages 4 to 5 years who were to receive an injected vaccine were randomly assigned to receive the original instructions or an abbreviated form of instructions of the W-B before and after the injection. The abbreviated instructions included two to three descriptive words from the original instructions placed under each facial expression. Before and after the injection, the child was asked, "Which face shows how much you hurt now"? T-tests were performed on the mean pre- and post-injection scores for the two groups. The mean post-injection score was significantly higher than the mean pre-injection score based on 95% confidence intervals for both groups. As noted by [redacted] this study supports the construct validity of the revised scale.

b(6)

Comments: The sponsor has attempted to justify the construct validity of the Wong-Baker FACES Pain Rating Scale with Modified Instructions by an internal validation assessment and by presenting data from the Nix study. Although the internal validation study appears to suggest that the modified instrument correlates with the VAS and FPS-R, the Nix study utilizes an entirely different set of instructions than the Wong-Baker FACES Pain Rating Scale with Modified Instructions and is not relevant.

In addition, the sponsor has not provided sufficient information to delineate the score change that would represent a clear treatment benefit. This is exhibited in the controlled clinical trials in which a responder definition was not identified a priori.

2.7 References

1. Wong D, Baker C. Pain in children: comparison of assessment scales. *Pediatric Nursing*. 1988; 14(1): 9-17.
2. Hicks C, et al. The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. *Pain* 2001; 93: 173-183.

3 BACKGROUND

To support the efficacy of the proposed indication, the sponsor submitted the data from two controlled pediatric studies conducted, 3268-3-003-1 and 3268-3-004-1. Both studies were multicenter, randomized, double-blind, sham placebo-controlled, single dose, and of parallel group design. Randomization at each site was stratified by age group (3 to 7 years, 8 to 12 years and 13 to 18 years), and subjects were evenly distributed across both genders. They were conducted in both outpatients undergoing phlebotomy as well as patients who were hospitalized for major or minor surgical or invasive diagnostic procedures. The objective of these studies was to evaluate in the pediatric population (3–18 years) the:

- Effectiveness of the Zingo for reducing the pain of venipuncture or peripheral venous cannulation
- Safety, skin tolerability and comfort of treatment with the Zingo

The site of administration study drug was determined by the investigator based on clinical need. Following treatment with the device, subjects were asked to score the comfort of device treatment using the Wong-Baker FACES Modified scale (all ages) and the 100 mm VAS (ages 8–18). Subjects underwent a post-administration dermal assessment for signs of erythema, edema, pruritus and hemorrhage/petechiae immediately after administration. Venipuncture or venous cannulation was performed at the site of administration 1 to 3 minutes post-administration. Following venipuncture or cannulation, all subjects were asked to rate the pain of the procedure using the Wong-Baker FACES-Modified (all ages) and the 100 mm VAS (ages 8–18). In addition, the subject’s parents/legal guardians were asked to assess the child’s pain following venipuncture or cannulation by completing a 100 mm VAS.

As noted by the sponsor, in both studies, the primary endpoint was met and treatment with the Zingo resulted in a statistically significant reduction of pain on venipuncture or peripheral venous cannulation compared to treatment with sham placebo, using the Wong-Baker FACES with Modified Instructions pain rating scale (Table 1).

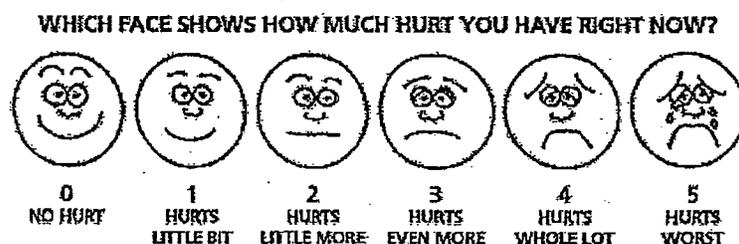
Table 1. Efficacy Results:

| Study Number | Primary Endpoint | Difference in LS Means (SE) | p-value |
|--------------|---|--------------------------------|---------|
| | Wong-Baker FACES Pain Score (LS mean) 3-18 years | | |
| 3268-3-003-1 | Zingo= 1.77 (n=292) Sham placebo= 2.10 (n=287) | -0.33 (0.13) | 0.0107 |
| 3268-3-004-1 | Zingo= 1.38 (n=269) Sham placebo =1.77 (n=266) | -0.39 (0.13) | 0.0034 |

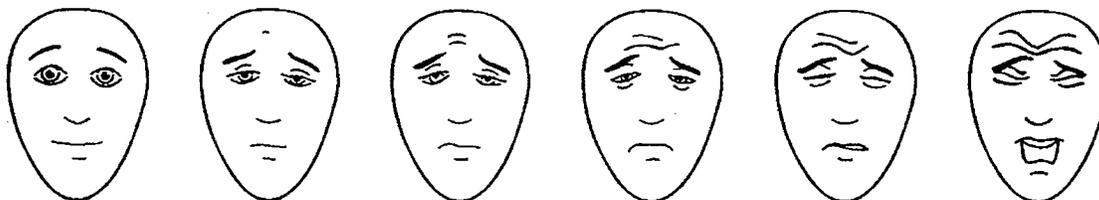
4 APPENDICES

4.1 Wong-Baker FACES Instrument

Explain to the person that each face is for a person who feels happy because he has no pain (hurt) or sad because he has some or a lot of pain. Face 0 is very happy because he doesn't hurt at all. Face 1 hurts just a little bit. Face 2 hurts a little more. Face 3 hurts even more. Face 4 hurts a whole lot. Face 5 hurts as much as you can imagine, although you don't have to be crying to feel this bad. Ask the person to choose the face that best describes how he is feeling.



4.2 Faces Pain Scale Revised Instrument:²



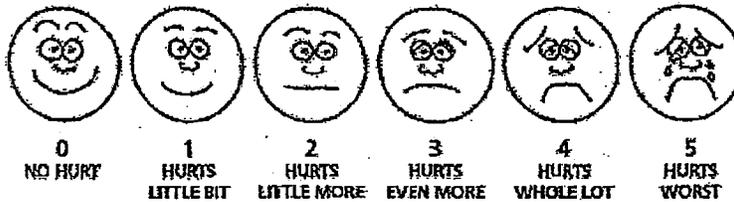
These faces show how much something can hurt. This face [point to the left-most face] shows no pain. The faces show more and more pain [point to each from left to right] up to this one [point to right-most face]—it shows very much pain. Point to the face that shows how much you hurt right now.

4.3 Wong-Baker Faces Instructions with Modified Instructions used in Zingo Pivotal Trials

INSTRUCTIONS "These faces show how much something can hurt. This face [point to the left-most face] shows no pain. The faces show more and more pain [point to each from left to right] up to this one [point to right-most face]—it shows a lot of pain. Point to the face that shows how much you hurt right now."

STUDY ENDPOINT REVIEW

WHICH FACE SHOWS HOW MUCH HURT YOU HAVE RIGHT NOW?



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/s/

Ann Marie Trentacosti
5/1/2007 02:59:03 PM
MEDICAL OFFICER

Laurie Burke
5/1/2007 06:27:40 PM
INTERDISCIPLINARY

| | | | | |
|--|---|---|--|---|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | REQUEST FOR SEALD CONSULTATION | | |
| TO (Division/Office): Study Endpoints and Label Development Team (SEALD) CDER/OND-IO White Oak Bldg 22, Mail Drop 6411 | | | FROM (Division/Office): Geri Smith, RPM, ODEII/DAARP, WO22, Room 3189 | |
| DATE of REQUEST 03-29-07 | NDA/BLA/IND NO. NDA 22-114 | SERIAL NO/SUPL. NO | TYPE OF DOCUMENT NDA | DATE OF DOCUMENT 11-21-06 |
| NAME OF DRUG Zingo (proposed) Dermal PowderJect Lidocaine HCl Delivery System | MEETING DATES FOR SUBMISSION Internal: Sponsor: | CLASSIFICATION OF DRUG Anesthetic | REQUESTED COMPLETION DATE 04-27-07 | |
| NAME OF SPONSOR or INVESTIGATOR (for investigator Initiated INDs): Anesiva | | | | |
| DRUG DEVELOPMENT PHASE & MILESTONE | | | | |
| <input type="checkbox"/> pre-IND/pre-BBIND <input type="checkbox"/> PHASE II <input type="checkbox"/> PHASE III <input type="checkbox"/> PRE-NDA/BLA MEETING | | <input checked="" type="checkbox"/> NDA/BLA/sNDA/SBLA REVIEW <input type="checkbox"/> NDA/BLA SAFETY/EFFICACY UPDATE <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> NDA/BLA/sNDA/SBLA RESUBMISSION REVIEW <input type="checkbox"/> ADVISORY COMMITTEE MEETINGS <input type="checkbox"/> LABELING (INITIAL OR REVISION) <input type="checkbox"/> ADVERTISING REVIEW | | <input type="checkbox"/> OTHER (Specify) |
| STUDY ENDPOINT OR LABELING To BE REVIEWED | | | | |
| STUDY ENDPOINT REVIEW | | | LABELING REVIEW | |
| <input type="checkbox"/> TYPE A MEETING PACKAGE <input type="checkbox"/> CLINICAL HOLD/DISPUTE RESOLUTION <input type="checkbox"/> SPA RESPONSE <input type="checkbox"/> TYPE B MEETING PACKAGE <input type="checkbox"/> PRE-IND MEETING <input type="checkbox"/> END OF PHASE II/Pre-PHASE III <input type="checkbox"/> PRE-NDA/BLA <input type="checkbox"/> TYPE C MEETING PACKAGE | | <input type="checkbox"/> SPECIAL PROTOCOL ASSESSMENT REVIEW <input type="checkbox"/> STANDARD PROTOCOL REVIEW <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> STATISTICAL ANALYSIS PLAN REVIEW <input type="checkbox"/> ENDPOINT DEVELOPMENT/VALIDATION DOSSIER <input checked="" type="checkbox"/> NDA / BLA REVIEW <input type="checkbox"/> AC MEETING | | <input type="checkbox"/> PROPOSED LABELING <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> OTHER (SPECIFY): |
| CONSULT REVIEW REQUESTED | | | | |
| <p>Please assess the acceptability of primary efficacy data obtained via use of the Wong-Baker-FACES pain scale diagram (shown below), with instructions validated for use with a different instrument, the Faces Pain Scale-Revised.</p> <p>Proposed Indication Zingo™ is a sterile, single-use, needle-free powder lidocaine delivery system (containing 0.5 mg lidocaine hydrochloride monohydrate) indicated for use on intact skin to provide local analgesia prior to venipuncture or intravenous cannulation.</p> <p><i>[Nearly all subjects were pediatric-age, in studies utilizing final and late-prototype devices. Approval during this review cycle, if granted, would most likely be only for pediatric use.]</i></p> <p>The primary efficacy measure (in pivotal trials), in all age groups, was the subject's assessment of pain, from venipuncture or intravenous cannulation one to three minutes after study drug administration. The pain assessment instrument was the Wong-Baker-FACES pain rating scale, a six-point scale anchored at zero ("No Hurt") and five ("Hurts Worst"), as shown below.</p> | | | | |



INSTRUCTIONS

"These faces show how much something can hurt. This face [point to the left-most face] shows no pain. The faces show more and more pain [point to each from left to right] up to this one [point to right-most face]—it shows a lot of pain. Point to the face that shows how much you hurt right now."

Figure 1: Wong-Baker FACES Pain Rating Scale

The instructions to subjects were modified from those in the original description of the Wong-Baker FACES instrument¹

Explain to the child that each face is for a person who feels happy because he has no pain (hurt) or sad because he has some or a lot of pain. Face 0 is very happy because he doesn't hurt at all. Face 1 hurts just a little bit. Face 2 hurts a little more. Face 3 hurts even more. Face 4 hurts a whole lot, but Face 5 hurts as much as you can imagine, although you don't have to be crying to feel this bad. Ask child to choose the face that best describes how he/she is feeling.

The instructions utilized throughout the Zingo development program were based on the Faces Pain Scale-Revised, as described and validated by Hicks².

These faces show how much something can hurt. This face [point to the left-most face] shows no pain. The faces show more and more pain [point to each from left to right] up to this one [point to right-most face]—it shows very much pain. Point to the face that shows how much you hurt right now.

At the pre-NDA meeting (6/19/2006), Anesiva stated that they "...mixed two traditional pain scales to use in their analyses because some literature reports showed that children prefer the modified faces scale for evaluation choices."

The company was told that they would need to submit an argument supporting their use of instructions from a different instrument (Faces Pain Scale-Revised), with the pain scale actually presented to subjects (Wong-Baker FACES instrument). Clarification would be expected, regarding why the combination (of instructions and instrument) had not been validated. Anesiva would also need to explain what the differences from (between) the two validated scales meant.

Appendix-C (EXPERT POSITION REGARDING VALIDATION SCALE) from the Summary of Clinical Efficacy (Module 2.7.3, pages 82 to 117), which is attached, contains the applicant's responses to the requests listed above. [The response appears only the last six pages. Most of the Appendix consists of the expert consultant's CV.]



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Please call Howard Josefberg, MO, at x61236 or Geri Smith, RPM, at x62204 with questions. Thanks.

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|---|--|
| SIGNATURE OF REQUESTER Geri Smith 03-29-07 | METHOD OF DELIVERY (Check one) DFS <input type="checkbox"/> INTEROFFICE MAIL <input type="checkbox"/> HAND-CARRIED <input type="checkbox"/> E-MAIL |
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

¹ Wong DL, et al: Whaley and Wong's Nursing Care of Infants and Children, ed. 5, St. Louis: Mosby; 1999.

² Hicks CL, et al. The Faces Pain Scale – Revised: toward a common metric in pediatric pain measurement. Pain. 2001;93:173-183.

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/s/

Geraldine Smith
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