CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208791Orig1s000

STATISTICAL REVIEW(S)
### STATISTICAL REVIEW AND EVALUATION

#### CLINICAL STUDIES

<table>
<thead>
<tr>
<th>NDA/Supplement #:</th>
<th>208-791</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Name:</strong></td>
<td>Chloroprocaine 1% (10 mg/ml) injection, HCl</td>
</tr>
<tr>
<td><strong>Indication(s):</strong></td>
<td>Spinal anesthesia</td>
</tr>
<tr>
<td><strong>Applicant:</strong></td>
<td>Sintetica SA</td>
</tr>
</tbody>
</table>
| **Date(s):**      | Letter date: August 26, 2016  
|                   | PDUFA date: August 28, 2017 |
| **Review Priority:** | Standard |
| **Biometrics Division:** | II |
| **Statistical Reviewer:** | Yan Zhou, Ph.D. |
| **Concurring Reviewer:** | David Petullo, M.S. |
| **Medical Division:** | Division of Anesthesia, Analgesia and Addiction Products |
| **Clinical Team:** |  
|                   | Medical Officer: Alla Bazini, M.D.  
|                   | Medical Team Leader: Leah Crisafi, M.D.  
|                   | Deputy Division Director: Rigoberto Roca, M.D. |
| **Project Manager:** | Selma Kraft |

**Keywords:** NDA review, clinical studies
# Table of Contents

1. EXECUTIVE SUMMARY .......................................................................................................................... 4  
2. INTRODUCTION ...................................................................................................................................... 4  
   2.1 OVERVIEW ........................................................................................................................................ 4  
   2.2 DATA SOURCES .................................................................................................................................. 5  
3. STATISTICAL EVALUATION ..................................................................................................................... 5  
   3.1 DATA AND ANALYSIS QUALITY ....................................................................................................... 5  
   3.2 EVALUATION OF EFFICACY ............................................................................................................. 6  
   3.3 EVALUATION OF SAFETY .................................................................................................................. 15  
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS ................................................................................. 15  
5. SUMMARY AND CONCLUSIONS ........................................................................................................... 15  
   5.1 STATISTICAL ISSUES ......................................................................................................................... 15  
   5.2 COLLECTIVE EVIDENCE .................................................................................................................... 16  
   5.3 CONCLUSIONS AND RECOMMENDATIONS ..................................................................................... 16  
   5.4 LABELING RECOMMENDATIONS ...................................................................................................... 16
LIST OF TABLES

Table 1: Summary of trials to be assessed in the statistical review ................................................................. 5
Table 2: Demographic and other baseline data for Study CHL1/02-2014 .......................................................... 7
Table 3: Patients with major protocol deviations in Study CHL1/02-2014 .......................................................... 8
Table 4: Rescue use in Study CHL1/02-2014 ..................................................................................................... 8
Table 5: Effectiveness of anesthesia and quality of spinal block in Study CHL1/02-2014...................................... 8
Table 6: Surgery duration (minutes) in Study CHL1/02-2014 ........................................................................... 9
Table 7: Time from intrathecal injection to surgery start (minutes) ................................................................. 10
Table 8: Reviewer’s results of primary efficacy endpoint in Study CHL1/02-2014............................................. 10
Table 9: Demographic and other baseline data for Study CHL1/02-2006/M .................................................... 12
Table 10: Patients excluded from the PP set in Study CHL1/02-2006/M ............................................................ 12
Table 11: Number of failures in Study CHL1/02-2006/M .................................................................................. 12
Table 12: Surgery duration (minutes) in CHL1/02-2006/M ............................................................................ 13
Table 13: Time from intrathecal injection to surgery start (minutes) ............................................................... 13
Table 14: Reviewer’s results of primary efficacy endpoint in Study CHL1/02-2006/M ..................................... 14
Table 15: Comparison of time to onset of sensory block at T10 between sex .................................................... 15
Table 16: Study CHL1/02-2006/M rescue use demographics ............................................................................. 15

LIST OF FIGURES

Figure 1: Graphical display of surgery duration data for each treatment group ................................................. 9
Figure 2: Graphical display of surgery duration data for chloroprocaine in Study CHL1/02-2006/M ............... 13
1. EXECUTIVE SUMMARY

Sintetica SA submitted a New Drug Application (NDA) for chloroprocaine hydrochloride (HCl) 1% (10 mg/ml) for intrathecal injection. The Applicant is seeking an indication for using as a spinal anesthesia in applicable surgical procedures. To support efficacy, 2 studies were reviewed, a phase 2 dose-finding, safety and pharmacokinetic study (CHL1/02-2014) and a phase 3 study (CHL1/02-2006/M). Study CHL1/02-2014 evaluated 3 doses of chloroprocaine HCl (30, 40 and 50 mg) in adult patients undergoing short duration elective surgery of the lower limb. Study CHL1/02-2006/M was a non-inferiority (NI) study comparing chloroprocaine 50 mg versus bupivacaine 10 mg in adult patients undergoing elective short duration (< 40 minutes) lower abdominal surgery.

The efficacy of chloroprocaine was evaluated by examining whether or not a patient required rescue medication to complete the surgical procedure. In the phase 2 Study CHL1/02-2014, all patients randomized to 50 mg chloroprocaine were able to complete surgery without the use of rescue medication. In the phase 3 Study CHL1/02-2006/M, 60 out of 66 patients (91%) randomized to chloroprocaine were able to complete the procedure without requiring rescue medication. Based on clinical interpretation and a similar failure rate noted for the control arm, chloroprocaine 50 mg was considered an appropriate dose for inducing spinal anesthesia by the clinical review team. Additionally, there were very few patients whose surgical procedure lasted longer than 40 minutes.

During the review of this NDA, it was determined that the primary efficacy endpoints in the reviewed studies were not indicative of successful spinal anesthesia. Time to complete regression of spinal block evaluated in Study CHL1/02-2014 may imply that there was a block but does not imply that the block provided adequate surgical analgesia. Similarly, onset time of sensory block at T₁₀ evaluated in Study CHL1/02-2006/M may indicate readiness for surgery but is only an indirect measure of a surgical level of analgesia.

Based on the information submitted and the clinical interpretation of efficacy, there are adequate efficacy data to support approval of the 50 mg dose for surgical procedures lasting less than 40 minutes.

2. INTRODUCTION

2.1 Overview

Chloroprocaine Hydrochloride (HCl), a local anesthetic (LA) synthesized from procaine, has been approved since 1955 and is currently marketed in the United States as Nesacaine (1% and 2%) and Nesacaine-MPF (2% and 3% methyl-paraben-free). Both products are indicated for use as a LA for infiltration, nerve block and epidural block. The applicant submitted the current NDA to seek an indication for use as a spinal anesthesia.
To support efficacy, the initial submission contained one phase 2 dose-finding, safety and pharmacokinetic (PK) study (Study CHL1/02-2014), one phase 3 efficacy and safety study (Study CHL1/02-2006/M) and one phase 4 post-marketing study. During the review process, it was noted that Study CHL1/02-2014 appeared to be identical to Study CHL1/02-2004 and was conducted after the phase 3 study was completed. Study CHL1/02-2004 was a phase 2 study conducted in Italy in 2005. An information request (IR) letter dated December 15, 2016 was sent out to inquire why the study was repeated and were there any differences between the studies. The applicant responded on December 23, 2016 and stated that Study CHL1/02-2004 did not evaluate PK, while Study CHL1/02-2014 (conducted at a different site) included the PK analysis and re-evaluated the possible clinical use of low-dose (30 mg), which was judged inappropriately during the previous study. Since Study CHL1/02-2004 did not contain information on surgical duration or time of intraoperative medication, it was not included in my review. My review focuses on Studies CHL1/02-2014 and CHL1/02-2006/M.

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Design*</th>
<th>Treatment/ Sample Size</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHL1/02-2014</td>
<td>SC, R, OB, PG, 3 doses trial</td>
<td>30 mg: 15</td>
<td>Primary: time to complete regression of spinal block</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 mg: 15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg: 15</td>
<td></td>
</tr>
<tr>
<td>CHL1/02-2006/M</td>
<td>MC, R, OB, NI trial</td>
<td>chloroprocaine:66 bupivacaine: 64</td>
<td>Primary: onset time of sensory block at T10</td>
</tr>
</tbody>
</table>


### 2.2 Data Sources

All data was supplied electronically as SAS transport files. The clinical study report is located at the following location in the CDER electronic document room (EDR):

`\CDSESUB1\evsprod\NDA208791\0001`

The datasets, define files, and programs are located in EDR at:

`\CDSESUB1\evsprod\NDA208791\0001\m5\datasets`

During the review process, the applicant submitted additional data regarding spinal duration, surgery duration and analgesia, anesthesia and sedation adjuncts for Study CHL1/02-2014 and Study CHL1/02-2006/M. However, the submitted data was in pdf files. To facilitate our review, an IR dated April 21, 2017 was sent out to ask for SAS transport data. The applicant responded on June 9, 2017 and the submitted data is located in EDR at:

`\CDSESUB1\evsprod\NDA208791\0021\m5\datasets`

### 3. STATISTICAL EVALUATION

#### 3.1 Data and Analysis Quality
The electronic datasets and define files submitted by the applicant were of acceptable quality, and were sufficient for validating study results.

3.2 Evaluation of Efficacy

3.2.1 Study CHL1/02-2014

Study Design and Endpoints

Study CHL1/02-2014 was a phase 2, single center, randomized, parallel-group, observer-blind, efficacy and PK study. The study was conducted from July 2015 until December 2015 in Bologna, Italy. The objective of the study was to evaluate the spinal anesthesia for three doses of chloroprocaine HCl 1% (30, 40 and 50 mg) in adult patients undergoing short duration elective surgery of the lower limb. Forty five patients were randomized equally prior to surgery. Sedation with midazolam was performed for all patients to reduce possible anxiety before the operation.

The primary efficacy endpoint, time to complete regression of spinal block, was defined as the time when Bromage score returned to 0 and sensitive perception returned to S1. Secondary efficacy endpoints included time to onset of sensory block, time to onset of motor block, time to readiness for surgery, time to unassisted ambulation, time to regression of sensory block to S1, sensory block metameric levels during the block, maximum level of sensory block, time to maximum level of sensory block, time to regression of two dermatomes with respect to the maximum level of sensory block, time to first spontaneous urine voiding, time to administration of rescue anesthesia or rescue analgesia, time to first post-operative analgesia, time to eligibility for home discharge, proportion of patients achieving effective anesthesia, quality of spinal block.

Statistical Methodologies

The statistical analysis of each efficacy endpoint was based on the full analysis set (FAS) which included all randomized patients who fulfilled the study protocol requirements in terms of study anesthetics administration. Each efficacy endpoint was also analyzed using the per protocol set (PP) which included all randomized patients who fulfilled the study protocol requirements in terms of anesthetic administration and primary efficacy evaluation, with no major deviations that could affect the primary efficacy results.

Based on discussions with the clinical review team, it was decided efficacy would be evaluated based on the number of patients requiring intraoperative rescue medication. Considering that the efficacy of chloroprocaine as an anesthetic agent is well established and there were 15 patients in each dose group, descriptive statistics for the intraoperative rescue use were reported. No formal statistical inferences were performed.

The applicant’s predefined primary efficacy endpoint was time to complete regression of spinal block. In the 74-day filing letter dated November 8, 2016, the Division stated that the primary endpoint does not reflect the ability of the drug to successfully produce surgical level of anesthesia. The applicant responded on January 20, 2017 and provided a rationale for the primary
endpoint. Even though we agree their chosen primary endpoint may imply that there was a block, it does not imply that the block provided adequate surgical analgesia.

To adjust for multiplicity, the applicant stated that the comparisons among three doses were performed according to the following hierarchical order:

1. Overall comparison;
2. 30 mg vs. 50 mg comparison;
3. 40 mg vs. 50 mg comparison;
4. 30 mg vs. 40 mg comparison.

Due to the small sample size, 15 patients per treatment arm, the overall comparison was analyzed using the Kruskal-Wallis test while pairwise comparisons between dose level groups were performed using the Wilcoxon rank-sum test. Missing values for time to complete spinal block regression (Tea) were replaced with the highest Tea detected in the corresponding treatment group. There were no replacements of missing values for the secondary efficacy endpoints.

**Patient Disposition, Demographic and Baseline Characteristics**

A total 45 patients equally received the study treatment as planned. One patient discontinued the study prior to treatment due to non-compliance.

The demographic and baseline characteristics for all randomized and treated patients are presented in Table 2.

<table>
<thead>
<tr>
<th>Table 2: Demographic and other baseline data for Study CHL1/02-2014</th>
<th>FAS set N=45</th>
<th>Chloroprocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female: n (%)</td>
<td>6 (40%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Male: n (%)</td>
<td>9 (60%)</td>
<td>9 (60%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (SD)</td>
<td>40.8 (12.1)</td>
<td>39.4 (12.5)</td>
</tr>
<tr>
<td>median (range)</td>
<td>42 (25-58)</td>
<td>41 (19-58)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mestizo: n (%)</td>
<td>1 (7%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>White: n (%)</td>
<td>14 (93%)</td>
<td>14 (93%)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (SD)</td>
<td>73.3 (14.1)</td>
<td>70.3 (13.3)</td>
</tr>
<tr>
<td>median (range)</td>
<td>78 (47-99)</td>
<td>66 (52-99)</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (SD)</td>
<td>172 (6.9)</td>
<td>170.2 (9.3)</td>
</tr>
<tr>
<td>median (range)</td>
<td>170 (158-185)</td>
<td>173 (153-185)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (SD)</td>
<td>24.7 (4.0)</td>
<td>24.2 (3.6)</td>
</tr>
<tr>
<td>median (range)</td>
<td>25.3 (18.8-30.6)</td>
<td>22.2 (19.0-30.6)</td>
</tr>
</tbody>
</table>

*Source: Clinical Study Report Table 14.1.1.3*
There were more male patients (60%) and the majority was white (96%). The mean age in years was 40.8, 39.4 and 41.5 in the 30 mg, 40 mg and 50 mg dose group respectively.

Results and Conclusions

The FAS set included 45 patients and the PP set included a subset of 39 patients. Six patients were excluded due to major protocol deviations which are listed in Table 3.

<table>
<thead>
<tr>
<th>Dose group</th>
<th>Subject</th>
<th>Major protocol deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg</td>
<td>S002/002</td>
<td>Received 30 oral drops of bromazepam 2.5 mg/ml solution before surgery</td>
</tr>
<tr>
<td>30 mg</td>
<td>S005/005</td>
<td>Received one additional dose of 2 mg of midazolam i.v. as rescue sedation</td>
</tr>
<tr>
<td>30 mg</td>
<td>S019/018</td>
<td>Underwent the surgery although T12 metameric level of sensory block was not achieved</td>
</tr>
<tr>
<td>40 mg</td>
<td>S020/019</td>
<td>Received one additional dose of 1 mg of midazolam i.v. due to patient’s anxiety</td>
</tr>
<tr>
<td>40 mg</td>
<td>S012/012</td>
<td>Underwent the surgery although T12 metameric level of sensory block was not achieved</td>
</tr>
<tr>
<td>50 mg</td>
<td>S003/003</td>
<td>Received 30 oral drops of bromazepam solution before surgery</td>
</tr>
</tbody>
</table>

Source: Reviewer’s analyses

The use of rescue medication is listed in Table 4. In the 50 mg dose group, there was no recorded use of rescue medication. However, in the FAS set, there were 3 patients in each of the 30 mg and 40 mg dose group that required rescue medication.

<table>
<thead>
<tr>
<th>Dose group</th>
<th>PP set</th>
<th>FAS set</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg</td>
<td>N=12</td>
<td>N=15</td>
</tr>
<tr>
<td>30 mg</td>
<td>N=13</td>
<td>N=15</td>
</tr>
<tr>
<td>30 mg</td>
<td>N=14</td>
<td>N=15</td>
</tr>
<tr>
<td>Administration of rescue medication (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to administration of rescue medication (mins) mean (SD)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Reviewer’s analyses

In the study, effective anesthesia was defined as the presence of adequate sensory and motor block, with adequate duration to cover surgery. Adequate spinal block was defined as that neither sedation nor analgesics was required to complete surgery. Inadequate spinal block was defined as that additional anesthesia or analgesia was required to complete surgery. Effectiveness of anesthesia and quality of spinal block are listed in Table 5. There were 100% of patients achieved an effective anesthesia with an adequate spinal block after receiving 50 mg chloroprocaine.

<p>| Reference ID: 4131483 |</p>
<table>
<thead>
<tr>
<th>Dose group</th>
<th>30 mg</th>
<th>40 mg</th>
<th>50 mg</th>
<th>30 mg</th>
<th>40 mg</th>
<th>50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=12</td>
<td>N=13</td>
<td>N=14</td>
<td>N=15</td>
<td>N=15</td>
<td>N=15</td>
</tr>
<tr>
<td>Effective and adequate</td>
<td>10 (83%)</td>
<td>12 (92%)</td>
<td>14 (100%)</td>
<td>12 (80%)</td>
<td>12 (80%)</td>
<td>15 (100%)</td>
</tr>
<tr>
<td>Ineffective and inadequate</td>
<td>2 (17%)</td>
<td>1 (8%)</td>
<td>0</td>
<td>3 (20%)</td>
<td>3 (20%)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Source:** Reviewer’s analyses

Per the request of the clinical review team, surgery durations for three dose groups were reported. Graphical display of surgery duration data for each treatment group is shown in Figure 1 and descriptive statistics are listed in Table 6. The average duration of surgery for the 50 mg dose group was 20 minutes with a maximum duration of 40 minutes.

**Table 6: Surgery duration (minutes) in Study CHL1/02-2014**

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
<th>≤ 30 mins</th>
<th>≤ 40 mins</th>
<th>≤ 60 mins</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg</td>
<td>25 (16)</td>
<td>22</td>
<td>9</td>
<td>74</td>
<td>87%</td>
<td>87%</td>
<td>93%</td>
</tr>
<tr>
<td>40 mg</td>
<td>20 (10)</td>
<td>17</td>
<td>7</td>
<td>40</td>
<td>87%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>50 mg</td>
<td>20 (8)</td>
<td>20</td>
<td>5</td>
<td>40</td>
<td>93%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Source:** Reviewer’s analyses

**Figure 1: Graphical display of surgery duration data for each treatment group**

**Source:** Response to IR dated February 17, 2017 Figure 1
Furthermore, the time from intrathecal injection to surgery start is summarized in Table 7. The average time for the 50 mg dose group was 22 minutes, with the minimum 11 minutes and maximum 42 minutes.

Table 7: Time from intrathecal injection to surgery start (minutes)

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg</td>
<td>19 (3)</td>
<td>19</td>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>40 mg</td>
<td>21 (5)</td>
<td>21</td>
<td>17</td>
<td>36</td>
</tr>
<tr>
<td>50 mg</td>
<td>22 (8)</td>
<td>20</td>
<td>11</td>
<td>42</td>
</tr>
</tbody>
</table>

*Source: Reviewer’s analyses*

For completeness, I also checked primary analyses and results are provided in Table 8. In the FAS set, the average time to complete regression of spinal block was 1.76, 2.13 and 2.23 hours in the 30 mg, 40 mg and 50 mg dose group respectively. There was no statistically significant difference between 40 and 50 mg in terms of primary efficacy endpoint. The dose of 30 mg significantly differed from the higher doses in time to regression of spinal block.

Table 8: Reviewer’s results of primary efficacy endpoint in Study CHL1/02-2014

<table>
<thead>
<tr>
<th>Analysis Set</th>
<th>PP set</th>
<th>FAS set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 mg</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>N=12</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>N=13</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>N=14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time to complete regression of spinal block (h)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Median (SD)</th>
<th>Median (SD)</th>
<th>Median (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 vs. 40 mg</td>
<td>1.81</td>
<td>2.12</td>
<td>2.22</td>
<td>1.76</td>
<td>2.13</td>
<td>2.23</td>
</tr>
<tr>
<td>vs. 50 mg</td>
<td>(0.33)</td>
<td>(0.39)</td>
<td>(0.39)</td>
<td>(0.35)</td>
<td>(0.46)</td>
<td>(0.38)</td>
</tr>
</tbody>
</table>

*Source: Reviewer’s analyses*

As all patients in the 50 mg dose group completed surgical procedures without using any rescue medication and the maximum of the surgical durations were 40 minutes. The study demonstrated the efficacy of 50 mg chloroprocaine for surgical procedures lasting less than 40 minutes.

**3.2.2 Study CHL1/02-2006/M**

**Study Design and Endpoints**
Study CHL1/02-2006/M was a phase 3, multicenter, randomized, observer-blind, NI study. The study was conducted from September 2007 until November 2008 in Europe. The objective of the study was to compare the performance of 50 mg of chloroprocaine 1% in intrathecal anesthesia versus 10 mg of bupivacaine 0.5%. Patients undergoing elective short duration (< 40 minutes) in low abdominal surgery (gynecology and urology disciplines) were randomized in a 1:1 ratio to receive either chloroprocaine or bupivacaine. Before anesthesia, if needed, systemic pre-medication with midazolam and/or local pre-anesthesia was performed.

The primary efficacy endpoint was the onset time of sensory block at T_{10}. Secondary efficacy endpoints included time to onset to motor block, maximum level of sensory block, resolution of sensory block to S1, resolution of motor block, time to unassisted ambulation, presence of urinary retention, time when patients asked the first time for analgesia and time to eligibility for home discharge.

**Statistical Methodologies**

The FAS set included all randomized patients who received the study drug and underwent surgery. The PP set included all randomized patients who fulfilled the study protocol requirements in terms of anesthetic administration and primary efficacy evaluation (time to achieve sensory block at T_{10}), with no major deviations that could affect the primary efficacy results. The PP set was used for the primary efficacy analysis.

As with Study CHL1/02-2014, the clinical review team considers efficacy to be established if a patient does not require intraoperative rescue medication. Considering that the efficacy of chloroprocaine as an anesthetic agent is well established, descriptive statistics for the intraoperative rescue use were reported. No formal statistical inferences were performed.

The applicant’s predefined primary efficacy endpoint was time to onset of sensory block at T_{10}. In the 74-day filing letter dated November 8, 2016, the applicant was informed that the Division does not think that the primary endpoint reflects the ability of chloroprocaine to successfully invoke anesthesia. According to the clinical review team, this endpoint is an indirect measure which may indicate readiness for surgery.

For completeness, I also checked the NI test in which the hypothesis was specified as:

\[ H_0: \mu_{\text{time of onset to } T_{10}, \text{test}} - \mu_{\text{time of onset to } T_{10}, \text{reference formulation}} > 4 \text{ min}, \]

\text{vs. the alternative hypothesis:}

\[ H_1: \mu_{\text{time of onset to } T_{10}, \text{test}} - \mu_{\text{time of onset to } T_{10}, \text{reference formulation}} \leq 4 \text{ min} \]

An independent two sample T-test was utilized to construct a 95% confidence interval for the difference between the two mean onset times of sensory block to T_{10}. If the upper limit of the confidence interval was less than 4 minutes, non-inferiority was established. In case of lack of normality of the underlying distributions, the Wilcoxon rank-sum test was used instead.
Patient Disposition, Demographic and Baseline Characteristics

Of the 135 patients that were screened, 130 were randomized. Five patients were not randomized either due to consent withdrawal or failing to continue to meet exclusion criterion.

The demographic and other background characteristics for all patients are presented in Table 9. The mean age was 45.2 and 50.6 years in the chloroprocaine and bupivacaine group respectively. Approximately 53% of patients were male and the majority of patients (95%) were white. There were no significant differences between two treatment groups with respect to age, weight, height, body mass index (BMI) and ASA physical status. The two treatment groups were significantly different in sex.

Table 9: Demographic and other baseline data for Study CHL1/02-2006/M

<table>
<thead>
<tr>
<th></th>
<th>Chloroprocaine</th>
<th>Bupivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 66</td>
<td>N = 64</td>
</tr>
<tr>
<td>Age: mean(SD)</td>
<td>45.2 (15.9)</td>
<td>50.6 (15.2)</td>
</tr>
<tr>
<td>Sex: male/female</td>
<td>42/24</td>
<td>27/37</td>
</tr>
<tr>
<td>Race: Caucasian/non-Caucasian</td>
<td>60/6</td>
<td>63/1</td>
</tr>
<tr>
<td>Weight: mean(SD)</td>
<td>71.4(11.9)</td>
<td>77.1(12.1)</td>
</tr>
<tr>
<td>Height: mean(SD)</td>
<td>168.4(7.2)</td>
<td>172.4(8.8)</td>
</tr>
<tr>
<td>BMI: mean(SD)</td>
<td>25.1(3.8)</td>
<td>25.9(3.3)</td>
</tr>
<tr>
<td>ASA physical status (I/II)</td>
<td>33/33</td>
<td>26/38</td>
</tr>
</tbody>
</table>

Source: Clinical Study Report Table 5

Results and Conclusions

The FAS set included 130 patients and the PP set included 121 patients out of the FAS set, with 9 patients excluded due to incomplete anesthesia or non-achievement of the anesthesia level required by the protocol. These 9 patients are listed in Table 10.

Table 10: Patients excluded from the PP set in Study CHL1/02-2006/M

<table>
<thead>
<tr>
<th>Dose group</th>
<th>Subject</th>
<th>Major protocol deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroprocaine</td>
<td>50 mg</td>
<td>Sensory block only to L1</td>
</tr>
<tr>
<td></td>
<td>203</td>
<td></td>
</tr>
<tr>
<td></td>
<td>205</td>
<td>No loss of sensation</td>
</tr>
<tr>
<td></td>
<td>104</td>
<td>Time to onset of sensory block at T10 not achieved</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>Treatment failure general anesthesia required</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>10 mg</td>
<td>Time to onset of sensory block at T10 not achieved</td>
</tr>
<tr>
<td></td>
<td>111</td>
<td>Time to onset of sensory block at T10 not achieved</td>
</tr>
<tr>
<td></td>
<td>204</td>
<td>Time to onset of sensory block at T10 not achieved</td>
</tr>
<tr>
<td></td>
<td>210</td>
<td>Intubation, no maximum level of sensory block after 20 minutes</td>
</tr>
<tr>
<td></td>
<td>220</td>
<td>Loss of pinprick sensation at T10 was not achieved, patient required add on medication for intraoperative analgesia</td>
</tr>
<tr>
<td></td>
<td>304</td>
<td>Spinal anesthesia did not achieve surgical level</td>
</tr>
</tbody>
</table>

Source: reviewer’s analyses

During the review process, failure was defined as using intraoperative rescue medications. The number of failures is listed in Table 11. In the FAS set, there were six patients using intraoperative rescue medications in each treatment group.

Table 11: number of failures in Study CHL1/02-2006/M

<table>
<thead>
<tr>
<th>Dose group</th>
<th>Chloroprocaine</th>
<th>Bupivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 4131483
Per the request of the clinical team, surgery duration was also summarized. Graphical display of surgery duration data for the chloroprocaine group is in Figure 2 and descriptive statistics are listed in Table 12. The average surgery duration for the 50 mg chloroprocaine group was 23 minutes, with 86% of patients having a time not greater than 40 minutes.

Table 12: Surgery duration (minutes) in CHL1/02-2006/M (FAS set)

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
<th>≤ 30 mins</th>
<th>≤ 40 mins</th>
<th>≤ 60 mins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroprocaine</td>
<td>23 (16)</td>
<td>20</td>
<td>3</td>
<td>78</td>
<td>80%</td>
<td>86%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Furthermore, the time from intrathecal injection to surgery start was summarized in Table 13. The average time for the 50 mg chloroprocaine group was 16 minutes, with the minimum 3 minutes and maximum 42 minutes.

Table 13: Time from intrathecal injection to surgery start (minutes)

|                  | Study CHL1/02-2006/M (FAS set) |
For completeness, the analysis results for primary efficacy endpoint are provided in Table 14. In the PP set, the average time to onset of sensory block at $T_{10}$ was 7.9 minutes in the chloroprocaine group and 9.4 minutes in the bupivacaine group. As data were not normally distributed, non-parametric Wilcoxon rank sum test was utilized and non-inferiority of chloroprocaine versus bupivacaine was proved.

Table 14: Reviewer’s results of primary efficacy endpoint in Study CHL1/02-2006/M

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Chloroprocaine 50 mg</th>
<th>Bupivacaine 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N =$</td>
<td>64</td>
<td>57</td>
</tr>
<tr>
<td>Time to onset of sensory block at $T_{10}$</td>
<td>$7.9 \pm 6.0$</td>
<td>$9.4 \pm 6.5$</td>
</tr>
</tbody>
</table>

Contrast | Non-parametric test
--- | ---
Chloroprocaine vs. Bupivacaine | $\mu_c - \mu_b \leq 4$

Non inferiority of chloroprocaine vs. bupivacaine proved

There was a concern with the NI aspect of this study. First, the primary endpoint is not considered clinical relevant. Second, the active control, bupivacaine, is not approved for use as a spinal anesthetic in the United States. Lastly, there is no justification for the chosen NI margin of four minutes. Even though the applicant stated that the selection of the non-inferiority margin was based on a combination of statistical reasoning and clinical judgement, it is not considered appropriate. Considering that the efficacy of chloroprocaine as an anesthetic agent is well established, there were numerous patients in both studies reviewed that were able to complete a surgical procedure without requiring rescue anesthesia, and bupivacaine is not approved for spinal anesthesia, the NI aspect of this study will only be considered as supportive in the sense that the pre-specified primary endpoint was met.

Even though there were six patients in the chloroprocaine arm that required intraoperative rescue medication, there were insufficient details regarding when these patients required rescue medication. The time of rescue medication was only known for two of the six patients. One of these two patients required general anesthesia and was obviously a failure. The other patient required fentanyl at 56 minutes. The other four patients required midazolam which may or may not qualify as rescue medication, i.e. administered to reduce anxiety. Based on this information and a similar number of patients requiring rescue medication in the control arm, the clinical review team deemed efficacy was established.
3.3 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Alla Bazini. The reader is referred to Dr. Bazini’s review for detailed information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The only subgroup analysis conducted by the applicant was an analysis of sex for the primary efficacy endpoint in Study CHL1/02-2006/M (Table 15). Based on this analysis, sex did not influence the time to onset of sensory block at $T_{10}$.

Table 15: Comparison of time to onset of sensory block at $T_{10}$ between sex

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Treatment</th>
<th>Wilcoxon rank sum test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female vs. Male</td>
<td>Overall</td>
<td></td>
<td>0.1568</td>
</tr>
<tr>
<td>Female vs. Male</td>
<td>Bupivacaine</td>
<td></td>
<td>0.9609</td>
</tr>
<tr>
<td>Female vs. Male</td>
<td>Chloroprocaine</td>
<td></td>
<td>0.1099</td>
</tr>
</tbody>
</table>

Source: Clinical Study Report Table 14.2.11

As we stated above, the efficacy of chloroprocaine was evaluated by examining whether or not a patient required rescue medication to complete the surgical procedure. In the phase 2 Study CHL1/02-2014, all patients randomized to 50 mg chloroprocaine were able to complete surgery without the use of rescue medication. In the phase 3 Study CHL1/02-2006/M, there were six patients using intraoperative rescue medication in each treatment group (Table 16). There were no clinically significant difference in age, sex and race between two groups.

Table 16: Study CHL1/02-2006/M rescue use demographics

<table>
<thead>
<tr>
<th>Subject</th>
<th>Arm</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Race</th>
</tr>
</thead>
<tbody>
<tr>
<td>203</td>
<td>C</td>
<td>18</td>
<td>F</td>
<td>Asian</td>
</tr>
<tr>
<td>205</td>
<td>C</td>
<td>72</td>
<td>F</td>
<td>White</td>
</tr>
<tr>
<td>211</td>
<td>C</td>
<td>56</td>
<td>F</td>
<td>White</td>
</tr>
<tr>
<td>202</td>
<td>C</td>
<td>53</td>
<td>M</td>
<td>White</td>
</tr>
<tr>
<td>212</td>
<td>C</td>
<td>45</td>
<td>M</td>
<td>White</td>
</tr>
<tr>
<td>121</td>
<td>C</td>
<td>64</td>
<td>M</td>
<td>White</td>
</tr>
<tr>
<td>107*</td>
<td>B</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>204</td>
<td>B</td>
<td>57</td>
<td>F</td>
<td>White</td>
</tr>
<tr>
<td>206</td>
<td>B</td>
<td>54</td>
<td>M</td>
<td>White</td>
</tr>
<tr>
<td>210</td>
<td>B</td>
<td>43</td>
<td>F</td>
<td>White</td>
</tr>
<tr>
<td>220</td>
<td>B</td>
<td>42</td>
<td>F</td>
<td>White</td>
</tr>
<tr>
<td>304</td>
<td>B</td>
<td>60</td>
<td>M</td>
<td>White</td>
</tr>
</tbody>
</table>

Source: Reviewer’s analyses. N/A: not available; C: chloroprocaine; B: bupivacaine

*Subject 107 was withdrawn from the study, no CRF was filled out

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues
There were two main statistical issues identified in the review of the two studies submitted to support the efficacy of chloroprocaine for spinal anesthesia. First, the primary efficacy endpoint for both studies was not clinically relevant. Second, the NI design of the phase 3 study was not appropriate as the active control, bupivacaine is not approved in the United States for spinal anesthesia and an acceptable NI margin is not available.

5.2 Collective Evidence

Based on clinical judgment, it was determined that the efficacy of chloroprocaine would be evaluated by examining whether or not a patient required rescue medication to complete the surgical procedure. In the phase 2 Study CHL1/02-2014, all patients randomized to 50 mg chloroprocaine were able to complete surgery without the use of rescue medication. In the phase 3 Study CHL1/02-2006/M, 60 out of 66 patients (91%) randomized to chloroprocaine were able to complete the procedure without requiring rescue medication. Additionally, since there were very few patients whose surgical procedure lasted longer than 40 minutes, the clinical review team is proposing to approve chloroprocaine 50 mg for surgical procedures lasting 40 minutes or less.

5.3 Conclusions and Recommendations

Based on the information submitted and the clinical interpretation of efficacy, there are adequate efficacy data to support approval of the 50 mg dose for surgical procedures lasting less than 40 minutes.

5.4 Labeling Recommendations

As the efficacy of chloroprocaine 50 mg was evaluated by the ability to complete the surgical procedure without using intraoperative rescue medication
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YAN ZHOU
07/28/2017

DAVID M PETULLO
07/28/2017
I concur.