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CLINICAL REVIEW(S)

CLINICAL REVIEW

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Drug Evaluation II

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Established Name Chloroprocaine Hydrochloride
Injection, 1 % (10 mg/mL)
(Proposed) Trade Name Clorotekal
Therapeutic Class Ester type local anesthetic
Applicant Sintetica S.A.

Formulation(s) 5 mL Type I clear glass ampoule
contains 50 mg of chloroprocaine
hydrochloride (10 mg/mL)
Dosing Regimen 50 mg (5 mL) single dose injection
Indication(s) For single intrathecal injection for the
production of subarachnoid block
(spinal anesthesia) to T10 in
patients undergoing surgical
procedures (b) (4)

Intended Population(s) Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This NDA contains adequate data to recommend approval of the 50 mg dose of Chloroprocaine Hydrochloride Injection, 1 % (10 mg/mL) for the indication of single intrathecal injection in adults for the production of subarachnoid block (spinal anesthesia) [REDACTED] (b) (4)

[REDACTED] (b) (4)

1.2 Risk Benefit Assessment

Although the number of subjects enrolled in the clinical studies conducted by the Sponsor is small, the Sponsor was able to provide additional safety data from their European postmarketing database, in addition to a thorough literature review of all pertinent studies that utilized intrathecal chloroprocaine. The literature highlights both common and uncommon adverse events associated with both intrathecal chloroprocaine, as well as, other local anesthetics given via intrathecal route (e.g., bupivacaine and lidocaine). All the data provided by the Sponsor appear to support that intrathecal chloroprocaine does not have a worrisome safety profile as compared to other local anesthetics used clinically. Chloroprocaine may also have a lower Transient Neurologic Symptoms (TNS) incidence than intrathecal lidocaine, and therefore, may be safer in that regard. Additionally, chloroprocaine has been approved in the United States since 1955 (Nesacaine) for administration via infiltration, peripheral nerve block, and epidural routes. It is widely used via epidural route in clinical practice, particularly in obstetric cases. Its safety profile via epidural route has been well established and is acceptable.

Other than the acceptable safety profile, the Sponsor's intrathecal chloroprocaine 1% has a particular advantage over the intrathecal gold standard, hyperbaric bupivacaine, because it has a shorter duration of action. Chloroprocaine may be a great alternative to general anesthesia for patients who are undergoing short, lower abdominal or lower extremity surgical procedures in both inpatient and outpatient settings. In particular, anesthesiologists who provide care at outpatient surgical centers, that often book multiple short procedures per day, may utilize intrathecal chloroprocaine in appropriate

subjects, without causing delay in surgical start or delaying patient recovery and discharge. A disadvantage of a short-acting spinal anesthetic like chloroprocaine is the inability of the anesthetic to provide pain control much beyond the operating room phase.

An additional risk to consider with intrathecal chloroprocaine is the possibility that the drug effect will wear off prior to completion of the surgery, which would require an anesthesiologist to administer another anesthetic, likely a general anesthetic, which they were trying to avoid in the first place. Because surgical durations vary from one surgery to the next and from one surgeon to another, it may be difficult to predict the actual length of surgery. Therefore, a certain amount of confidence in the surgical time must exist prior to consideration of intrathecal chloroprocaine. (b) (4)

The analysis of the data available from all studies conducted by the Sponsor lead to a conclusion that 50 mg of chloroprocaine is appropriate for surgical procedures that last < 40 minutes. This would then create a “buffer” for the time of intrathecal injection to the time of actual surgical incision (often 20 minutes or longer), and will decrease the likelihood that the spinal block would wear off prior to completion of the surgery.

Additional doses of intrathecal chloroprocaine (30 mg and 40 mg) were analyzed in the Phase 2 studies. Due to the limited number of subjects in these dose cohorts, their efficacy is not well characterized, and the clinical impracticability of needing a spinal anesthetic that lasts significantly less than 40 minutes, these doses are not considered to offer any additional benefit, and therefore, are not recommended for approval.

Given the time constraints discussed, there may be few situations where intrathecal chloroprocaine would be of clinical benefit. However, given the favorable safety profile of the Sponsor’s intrathecal chloroprocaine 1%, it is reasonable to believe that the 50 mg intrathecal chloroprocaine dose would have clinical utility.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

At present there is no need for any postmarketing risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

Pediatric Research Equity Act (PREA) applies to this NDA. Under PREA, the Sponsor should be required to conduct studies to assess safety, efficacy, and appropriate dosing

regimens for intrathecal chloroprocaine in pediatric subjects. The studies should begin as soon as study protocols are agreed upon with the Agency.

From the clinical perspective, no additional PMRs are indicated.

2 Introduction and Regulatory Background

2.1 Product Information

Chloroprocaine hydrochloride (HCl) was first synthesized in 1946 from procaine. Chloroprocaine was first approved by the FDA in 1955 (NDA 009435 (Nesacaine)) for production of local anesthesia by infiltration, peripheral nerve block (PNB), and lumbar and caudal epidural blocks.

On March 19, 2012, marketing authorization was obtained from the German Authority for Sintetica's Ampres® 1% for intrathecal administration (based on published literature plus nonclinical and clinical trials sponsored by Sintetica S.A.). Currently, chloroprocaine HCl 1% for intrathecal administration (under the brand names of Ampres/Clorotekal/Decelex) is registered in 9 European countries (Germany, Austria, France, Belgium, Spain, UK, Ireland, Poland and Italy). In these countries, chloroprocaine 1% is currently licensed for intrathecal anesthesia in adults where the planned surgical procedure is not expected to exceed 40 minutes.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are two local anesthetics (lidocaine and bupivacaine) that have formulations which are currently approved for intrathecal injection in the United States. More specifically, these are:

- lidocaine 1.5% with dextrose 7.5% (NDA 016297) – no longer manufactured
- lidocaine 5% with dextrose 7.5% (ANDA 083914)
- bupivacaine 0.75%
 - o NDA 018692 (Marcaine)
 - o ANDA 207266
 - o ANDA 071810
 - o ANDA 071202 (Sensorcaine) – no longer manufactured

Table 1 below is adapted from an article entitled “Spinal Anesthesia” on New York School of Regional Anesthesia (NYSORA) website. It lists the commonly and less commonly used local anesthetics (both approved and off-label) for the production of subarachnoid block. (NYSORA.COM, 2013)

Table 1 Dose, Duration, and Onset of Local Anesthetics Used in Spinal Anesthesia

	Dose (mg)		Duration (min) Plain	With 0.2mg Epinephrine	Onset (min)
	to T10	to T4			
Commonly Used					
Lidocaine 5%	50–75	75–100	60–70	75–100	3–5
Bupivacaine 0.75%	8–12	14–20	90–110	100–150	5–8
Less Commonly Used					
Tetracaine 0.5%	6–10	12–16	70–90	120–180	3–5
Mepivacaine 2%	N/A	60–80	140–160	N/A	2–4
Ropivacaine 0.75%	15–17	18–20	140–200	N/A	3–5
Levobupivacaine 0.5%	10–15	N/A	135–170	N/A	4–8
Chloroprocaine 3%	30	45	80–120	130–170	2–4

(Source: NYSORA.COM, 2013)

2.3 Availability of Proposed Active Ingredient in the United States

Chloroprocaine is currently approved in the United States for indications that include local anesthesia by infiltration, PNB, and lumbar and caudal epidural blocks. No chloroprocaine products are currently approved for intrathecal injection.

The following NDA and ANDAs are approved in the United States:

- NDA 009435 approved in 1955 (Fresenius Kabi USA)
 - o Nesacaine® (1% and 2%)
 - Multidose vials with methylparaben as preservative
 - Indicated for production of local anesthesia by infiltration and PNB
 - o Nesacaine®-MPF (2% and 3% 'methyl-paraben-free')
 - Single dose vials without preservative and without Ethylenediaminetetraacetic acid (EDTA)
 - Indicated for the production of local anesthesia by infiltration, peripheral and central nerve block, including lumbar and caudal epidural blocks
- ANDA 040273 (chloroprocaine hydrochloride 2%, 3%), ANDA 087446 (chloroprocaine hydrochloride 3%), ANDA 087447 (chloroprocaine hydrochloride 2%)
 - o Indicated for the production of local anesthesia by infiltration, peripheral and central nerve block, including lumbar and caudal epidural blocks

2.4 Important Safety Issues With Consideration to Related Drugs

Neurologic complications are the most important safety issue with intrathecal local anesthetic administration. Several literature studies have evaluated various neurological complications in association with intrathecal local anesthetics. A Cochrane Database review from 2009 looked at sixteen clinical trials (1467 patients) and reported that 125 patients developed TNS. The authors concluded that the “relative risk (RR) for developing TNS after spinal anaesthesia [sic] with lidocaine as compared to other local anaesthetics [sic] (bupivacaine, prilocaine, procaine, levobupivacaine, ropivacaine, and 2-chloroprocaine) was 7.31 (95% confidence interval (CI) 4.16 to 12.86). Mepivacaine was found to give similar results as lidocaine and was therefor [sic] omitted from the overall comparison to diminish the heterogeneity.” (Zaric, 2009)

Table 2 Risk Ratio of Lidocaine versus Other Local Anesthetics in Production of TNS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Transient Neurologic Symptoms	16	1467	Risk Ratio (M-H, Random, 95% CI)	4.62 [2.30, 9.26]
1.1 Bupivacaine	7	621	Risk Ratio (M-H, Random, 95% CI)	6.65 [2.05, 21.56]
1.2 Mepivacaine	3	182	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.15, 7.45]
1.3 Prilocaine	4	414	Risk Ratio (M-H, Random, 95% CI)	5.62 [2.07, 15.23]
1.4 Procaine	2	130	Risk Ratio (M-H, Random, 95% CI)	6.94 [1.94, 24.86]
1.5 Ropivacaine	1	45	Risk Ratio (M-H, Random, 95% CI)	5.81 [0.25, 134.73]
1.6 Levobupivacaine	1	45	Risk Ratio (M-H, Random, 95% CI)	9.69 [0.49, 189.93]
1.7 2-Chlorprocaine	1	30	Risk Ratio (M-H, Random, 95% CI)	11.00 [0.66, 182.87]

(Source: Zaric, 2009)

There are literature reports of neurological toxicity following inadvertent intrathecal injections of chloroprocaine during attempted epidural administration which resulted in prolonged sensory and motor block. Winnie et. al., reported eight obstetric patients that had neurologic adverse events from unintentional dural puncture with either 2 or 3% chloroprocaine. Although in most of these cases the deficits resolved after six to twelve weeks, several neurological disturbances were persistent, with one patient that developed chronic adhesive arachnoiditis. (Winnie, 2001)

“Thorough laboratory studies consequently discovered that a combination of low pH and sodium bisulfite (the antioxidant) in the Nesacaine formulation was the cause of the neurologic injuries. A Food and Drug Administration (FDA) panel specifically convened to address this issue concluded that the drug 2-chloroprocaine itself was no more neurotoxic than lidocaine, bupivacaine, or mepivacaine.” (Warren, 2004)

In 1987, the results of studies implicating sodium bisulfite as the cause of neurological deficits associated with intrathecal injection of chloroprocaine, led to newer formulations of the drug that included calcium EDTA. This new preparation was called Nesacaine-MPF (methylparaben-free). However, this led to higher than expected incidence of muscular back pain following epidural anesthesia. Since the incidence of muscular back pain appeared to be related to volume injected and during use for skin infiltration, the muscular back pain was attributed to possible tetany in the paraspinal muscles caused by calcium binding by the EDTA. (Winnie, 2001)

Since 1996, plain formulations, without preservative or EDTA, of chloroprocaine have been on the United States market. No major safety concerns have been reported with the new formulations.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On March 19, 2012, marketing authorization was obtained from the German Authority for Sintetica's Ampres® 1% for intrathecal administration. This approval was based on published literature plus nonclinical and clinical trials sponsored by Sintetica SA.

Since March 2012, Chloroprocaine HCl 1% (10 mg/mL) Injection, USP has been approved in several European countries for spinal anesthesia in adults where the planned surgical procedure should not exceed 40 minutes. Chloroprocaine HCl 1% has been sold with trade name of AMPRES®, Cholorotekal®, or Decelex® in the following countries: Great Britain, Poland, Italy, Ireland, France, Spain, Germany, Belgium and Austria.

Table 3 Regulatory Timeline and Events

Meeting/Communication/Date (Supporting Document)	Event/Key Clinical Issues
PIND 119674/Teleconference with (b) (4) Sintetica SA December 17, 2013	NDA 009435 (Nesacaine®) is an acceptable listed drug to reference in a 505(b)(2) application. • The Sponsor must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). • The Sponsor should establish a "bridge" (e.g., via comparative bioavailability data) between the

	proposed drug product and each listed drug upon which they propose to rely on. • The Sponsor can consider conducting a study to obtain PK information of their product, and then compare its systemic exposure to NDA 009435. • If the Sponsor is unable to produce PK data for the listed drug, information in the literature could be used for bridging their product to the listed drug, provided that the proposed listed drug is used in the studies reported in the literature, and the quality of the data from the literature is acceptable based on the Agency's current standards. Indication should be "for intrathecal injection in adults for the production of subarachnoid block (spinal anesthesia)." NDA submission should include: final study reports with full protocols and datasets for the studies conducted by Sponsor, documentation of efforts made to obtain original protocols and data for the studies reported in the published literature, postmarketing safety data, integrated summaries of safety and efficacy. The proposed dosing should be as specific as possible for a given clinical situation and patient population. Since an intrathecal route of administration for chloroprocaine is novel, adequate GLP toxicology studies in two species (at least one non-rodent) that employ the proposed intrathecal route of administration will be required to support clinical studies.
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See Section 9.4 of this review for pertinent regulatory events during the review cycle.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the original NDA submission was organized, enabling locating the clinical information necessary to start the clinical review process. However, although upon filing the clinical data appeared complete, it became apparent that the Sponsor did not include a previously-conducted Phase 2 study (CHL1/02-2004). Specifically, this study was later repeated, with an additional PK component, by the Sponsor as study CHL1/02-2014, which had a lower incidence of subjects requiring intraoperative rescue medications than the original Phase 2 study. The Sponsor did not disclose this information in the original NDA submission.

In addition, upon review of the datasets provided, it became apparent that critical data on times of surgical procedure start, surgical procedure end, and timing of rescue medications was missing or only partially complete for the two studies originally submitted to the NDA (CHL1/02-2006/M and CHL1/02-2014). Given that the primary efficacy endpoints chosen for these studies did not evaluate the ability of the drug to provide adequate anesthesia for the surgical procedure, and post-hoc analyses were needed in order to ascertain efficacy of the study drug, several interactions with the Sponsor took place (via Information Requests that are outlined in Section 9.4) before these issues were addressed satisfactorily.

It took several months of communications with the Sponsor, with several large amendments submitted as a result, which included clinical study reports (CHL1/02-2004 and CHL1/01-2012/M), revised Integrated Summary of Effectiveness (ISE), Case Report Forms (CRFs) for every subject in every study, as well as operating room (OR) records for every subject in every study. Due to these amendments, in particular, the submission containing CRFs for each patient in each study, a decision was made to extend the review clock.

3.2 Compliance with Good Clinical Practices

The Sponsor has stated that all clinical studies provided in this submission were conducted in compliance with Good Clinical Practices.

However, upon in depth review of Phase 3 study (CHL1/02-2006), which was conducted at four clinical sites, it became apparent that one clinical site (Marburg, Germany), had significantly higher rates of failure in treatment and control arms, defined as need for intraoperative rescue medications for anxiety or analgesia. Since the Marburg site was only the third highest enroller (20 out of a total of 130 subjects enrolled in the study), Office of Scientific Investigations (OSI) was not planning on inspecting this site. After

the discrepancy in efficacy data was uncovered, OSI was asked to inspect the Marburg site, in addition to the two highest enrolling sites (Lugano, Switzerland, and Parma, Italy) in order to detect a problem with data integrity. OSI inspection report is still pending but OSI's preliminary assessment is that their inspection findings would not preclude approval.

3.3 Financial Disclosures

The Sponsor certified that none of the clinical investigators disclosed a proprietary interest in the product or a significant equity in the Sponsor. Refer to Section 9.5 of this review for the clinical investigator financial disclosure.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The review team included Drs. Valarie Amspacher, Ciby Abraham, and Julia Pinto. They have not identified any issues that would preclude approval of chloroprocaine 1% at this time.

4.2 Clinical Microbiology

A Clinical Microbiology review not required for this NDA.

4.3 Preclinical Pharmacology/Toxicology

The review team included Drs. Imran Khan, Jay Chang, and Dan Mellon. Although they have not recommended approval, they did not identify any toxicological issues that would preclude approval of chloroprocaine 1% at the time of finalization of this review. A long-term repeat dose toxicity study may be given as a post-marketing requirement.

4.4 Clinical Pharmacology

The review team included Drs. Srikanth Nallani and Yun Xu. They have reviewed the Phase 2 pharmacokinetic study, CHL1/02-2014, in addition to published literature. They did not identify any issues that would preclude approval of chloroprocaine 1% at the time of finalization of this review.

4.4.1 Mechanism of Action

Chloroprocaine, like other local anesthetics, blocks the generation and the conduction of nerve impulses. Chloroprocaine acts by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the nerve action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

4.4.2 Pharmacodynamics

The Sponsor did not perform any analyses regarding pharmacodynamics of chloroprocaine and is relying upon the following information in the Nesacaine package insert (verbatim):

Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems. At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block and ultimately to cardiac arrest. In addition, with toxic blood concentrations myocardial contractility may be depressed and peripheral vasodilation may occur, leading to decreased cardiac output and arterial blood pressure.

Following systemic absorption, toxic blood concentrations of local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central stimulation may be manifested as restlessness, tremors and shivering, which may progress to convulsions. Depression and coma may occur, possibly progressing ultimately to respiratory arrest.

However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior stage of central nervous system stimulation.

4.4.3 Pharmacokinetics

The following information is proposed by the Sponsor for the pharmacokinetic section of the chloroprocaine label. It is taken directly from the Nesacaine label, with minor wording modifications performed by Sponsor.

The rate of systemic absorption of local anesthetic drugs is dependent upon the total dose concentration of drug administered, the route of administration, the

vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic injection.

The onset of action with chloroprocaine is rapid (usually 6 to 12 minutes), and the duration of anesthesia, depending upon the amount used and the route of administration.

Local anesthetics appear to cross the placenta by passive diffusion. However, the rate and degree of diffusion varies considerably among the different drugs as governed by: (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, since only the free, unbound drug is available for placental transfer. Thus, drugs with the highest protein binding capacity may have the lowest fetal/maternal ratios. The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, nonionized drugs readily enter the fetal blood from the maternal circulation.

Distribution

Depending upon the route of administration, local anesthetics are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain. Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic or renal disease, addition of epinephrine, factors affecting urinary pH, renal blood flow, the route of administration, and the age of the patient.

Chloroprocaine plasma half-life in vitro is about 25 seconds, whereas the apparent half-life in vivo was found to be 3.1 ± 1.6 min (range 1.5 – 6.4 min) in maternal plasma after intrapartum epidural anesthesia.

Metabolism

Chloroprocaine is rapidly metabolized in plasma by hydrolysis of the ester linkage by pseudocholinesterase. The hydrolysis of chloroprocaine results in the production of β -diethylaminoethanol and 2-chloro-4-aminobenzoic acid, which inhibits the action of the sulfonamides.

Excretion

The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH.

The following language was added to the proposed label by the Sponsor regarding chloroprocaine elimination and distribution from the CSF (verbatim):

(b) (4)

(b) (4)

Pharmacokinetics after intrathecal administration

Plasma concentrations of chloroprocaine and 2-chloro-4-aminobenzoic acid (ACBA) after intrathecal administration

(b) (4)

Table (b) (4) PK Variables: Plasma Concentrations (ng/mL) of Chloroprocaine and ACBA

Analyte	Chloroprocaine	ACBA
	(b) (4) 50 mg	(b) (4) 50 mg
Dose group	N=15	N=15
Pre-dose (0)	BLQL	BLQL
5 min post-dose	BLQL	24.887±20.340
10 min post-dose	BLQL	75.833±67.635
30 min post-dose	BLQL	97.647±61.704
60 min post-dose	BLQL	78.380±48.403

Mean ± SD is shown; BLQL: below the quantification limit (4.0 ng/mL)

Specific Populations

The Sponsor did not conduct studies in subjects with hepatic impairment or renal impairment. The following language (b) (4) is included in the proposed labeling for intrathecal chloroprocaine:

(b) (4)

Renal Impairment

(b) (4) chloroprocaine is known to be substantially excreted by the kidney, (b) (4)

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5 provides a list of clinical studies completed by the Sponsor that were utilized to assess both safety and efficacy of 1% chloroprocaine for the proposed indication.

Table 5 Summary of Studies

	CHL1/02-2004 (Phase 2)	CHL1/02-2014 (Phase 2)	CHL1/02-2006/M (Phase 3)	CHL1/01-2012/M (Phase 4)
Study Design	Prospective, randomized, parallel-group, observer-blind, single-center, dose-response	Prospective, randomized, parallel-group, observer-blind, single-center, dose-response	Prospective, randomized, blind-observer, multicenter, non-inferiority	Prospective, open-label, single-arm, multicenter observational
Primary Efficacy Endpoint or Primary Objective	Time to regression of spinal block (i.e., end of anesthesia)	Time to regression of spinal block (i.e., end of anesthesia)	Non-inferiority of chloroprocaine 1% (50 mg) versus bupivacaine 0.5% (10 mg) in terms of onset time of sensory block at T10 (assessed by the loss of pin-prick sensation) in minutes (margin: 4 minutes)	To evaluate relationship between spinal block with chloroprocaine 1% and the onset of all possible neurological adverse events, specifically TNS and CES
Treatments	Three doses of chloroprocaine 1% have been administered: 3, 4, and 5 ml of solution, corresponding to	Three doses of chloroprocaine 1% have been administered: 3, 4, and 5 ml of solution, corresponding to	<u>Treatment Group:</u> 5 ml of chloroprocaine 1% hydrochloride (50mg) was administered as	Dose of intrathecal chloroprocaine 1% is not fixed but determined by the

	30mg, 40mg, and 50 mg of the drug. Each dose has been administered as a single-shot spinal injection.	30mg, 40mg, and 50 mg of the drug. Each dose has been administered as a single-shot spinal injection.	single-shot spinal injection. <u>Reference Group:</u> 2 ml of 0.5% bupivacaine (10 mg) was administered as single-shot spinal injection.	investigator for each surgery based on the nature of surgery in accordance with European-approved labeling.
Number of Subjects Dosed	44	45	1% chloroprocaine 50 mg: 66 0.5% bupivacaine 10 mg: 64	392

5.2 Review Strategy

The focus of this NDA review was on the following items:

- Findings of the studies conducted by the Sponsor to address the efficacy of (b) (4) 50 mg) of chloroprocaine 1% for intrathecal administration.
 - After in-depth review of all data submitted by the Sponsor, a (b) (4) the focus of this review is primarily on 50 mg dose (See Section 6.1.1 for more details).
- Findings of the studies conducted by the Sponsor to address the safety of intrathecal chloroprocaine 1%.
- Post-marketing European safety and efficacy data submitted by the Sponsor.
- Safety data collected from literature by the Sponsor.

5.3 Discussion of Individual Studies/Clinical Trials

The following is a summary of the background information pertinent to each study. Specific details of each study are discussed, as appropriate, in the sections below.

- Study CHL1/02-2004 is titled "Spinal Anesthesia with 2-Chloroprocaine 1% for Lower Limb Procedures of Short Duration: A Prospective, Randomized, Blind, Dose-finding Study."
 - Conducted between March 2005 and June 2005 at University Hospital of Parma, Italy.

- This dose-response and safety study was the first Phase 2 study conducted to evaluate the efficacy of three chloroprocaine 1% doses (30mg, 40mg, and 50mg) and was used as part of the development of chloroprocaine 1% for intrathecal injection for the European registration.
- This study was originally presented in the NDA as a literature reference only. The literature reference did not contain detailed study results, particularly the use of rescue medications in the operating room.
- Due to the small safety and efficacy database in the two studies submitted as part of the original NDA, the Sponsor was asked to submit all datasets and Clinical Study Report (CSR) for this study. Although the Sponsor was unable to provide original datasets from the study, the CSR and all Case Report Forms (CRFs) (both in Italian and translated to English) were submitted. Operating room (OR) records were also submitted, but were illegible. However, the Sponsor was able to examine the OR records and CRFs in order to provide information on time of chloroprocaine administration, use of intraoperative rescue medications, and estimate the time of their administration +/- 15 minutes, as well as, estimate surgical duration +/- 15 minutes.
 - o Given the nature of the data, particularly the higher rate of failures seen in this study, it was determined that it should be included in the efficacy database and analysis. However, because the surgical durations were roughly estimated, this data could not be used to determine the appropriateness of the proposed length of surgical duration by the Sponsor.
 - o In addition, since the CRFs were complete and legible, this study was also used to contribute to the overall safety analysis of this review.
- In addition, the Sponsor was asked to provide a list of differences between this study and the second Phase 2 study (CHL1/02-2014), and to provide a rationale for the difference in outcomes with respect to need for rescue analgesia and anxiety medications in the operating room. The Sponsor provided a summary describing the differences between the two studies, with the following pertinent information:
 - o Study CHL1/02-2004 did not evaluate pharmacokinetics
 - o Study site: CHL1/02-2004 was conducted in Parma, Italy, whereas study CHL1/02-2014 was conducted in Bologna, Italy, because the Bologna site was able to accommodate and manage blood sampling required in the second study.
 - o Time to end of anesthesia (T_{ea}) was longer after all 3 doses in CHL1/02-2014. No differences in time to readiness for surgery was detected between the two studies.

- Study CHL1/02-2004 had more subjects requiring rescue medications (see Table 6 below) because average surgical procedure length was longer in study CHL1/02-2004. Study inclusion criteria support this:
 - CHL1/02-2004: Lower limb surgery < 60 min
 - CHL2/02-2014: Lower limb surgery < 40 min

Table 6 Number of Subjects Requiring Intraoperative Rescue Medications in Phase 2 Studies

Dose Cohort	CHL1/02-2004	CHL1/02-2014
30 mg	7	3
40 mg	5	2
50 mg	2	0

2. Study CHL1/02-2014 is titled “Spinal Anesthesia with Chloroprocaine HCl 1% for Elective Lower Limb Procedures of Short Duration: A Prospective, Randomized, Observer-blind Study in Adult Patients.”

- Conducted between July 2015 and December 2015 at the Rizzoli Orthopedic Institute in Bologna.
- This was the second dose-finding, safety, and pharmacokinetic study because the original study (CHL1/02-2004) lacked pharmacokinetic component requested by the FDA during the pre-IND interaction. An additional goal of the study was to evaluate the clinical utility of the low-dose 30 mg of chloroprocaine 1%, which was judged to be inappropriate in study CHL1/02-2004.
- Since times of surgical start and surgical end were not included in the datasets, the Sponsor was asked to provide all OR records and CRFs for each subject in the study. (b) (4)

[REDACTED] this information was needed to provide verification for all intraoperative rescue medications, since the Sponsor’s definition of rescue did not align with the FDA definition (i.e., Sponsor did not consider additional doses of intraoperative midazolam as rescue medication, whereas the FDA considers additional doses of midazolam may be attributed to intraoperative pain that leads to additional intraoperative anxiety).

- The Sponsor submitted all OR records, which were illegible. The Sponsor also submitted all CRFs, which were in English and legible. The CRFs had pertinent surgical times recorded.
3. Study CHL1/02-2006/M is titled “Prospective, Blind-observer, Randomized Clinical Study to Investigate and Compare the Efficacy of Intrathecal Plain Solutions Containing Chloroprocaine 1% (50 mg) versus Bupivacaine 0.5% (10 mg) (10 mg)
- Enrolled subjects underwent elective short-duration (< 40 minutes) lower abdominal surgical procedures (gynecology and urology disciplines) that required T10 metameric level of sensory block and identical anesthesia procedures.
 - This was a non-inferiority study that compared chloroprocaine 1% (50 mg) to bupivacaine 0.5% (10 mg) in terms of onset time of sensory block at T10 (assessed by the loss of pin-prick sensation) in minutes (margin of 4 minutes).
 - Although time of chloroprocaine injection and the names of rescue medications given in the operating room were documented in the datasets provided, times of the rescue medication administration, as well as, times of surgical procedure start and surgical procedure end were not apparent. When asked to provide this data, the Sponsor submitted CRFs that contained information on time of surgical procedure start and finish, however, did not contain time of intraoperative rescue medications. The Sponsor was then asked to review OR records (also provided, but illegible) in order to discern the approximate time of intraoperative rescue medications. The Sponsor was able to provide estimated time of most intraoperative rescue medications +/- 15 minutes.
4. Study CHL1/02-2012/M (European Post-Authorization Safety Study (PASS))
- Conducted between November 2013 and October 2016.
 - This is a Phase 4, prospective, multicenter, observational study to evaluate the relationship between intrathecal chloroprocaine 1% and the occurrence of possible neurological adverse events, with particular attention to Transient Neurological Symptoms (TNS) and Cauda Equina Syndrome (CES) in patients undergoing short surgical procedures (< 40 minutes).
 - The follow-up questionnaire specifically designed was filled out at 24 hours and 7 days after spinal injection of chloroprocaine in order to gather possible neurological complications. Using this questionnaire, the Investigators interviewed subjects about their symptoms, neurological symptoms (indicative of TNS, CES), pain at site of chloroprocaine injection, and pain at the site of surgery, rated on a scale from 0 to 10 for pain intensity. Other adverse events (AEs) were also assessed. In cases of suspected neurological adverse events, the Investigators were

requested to perform a complete diagnostic evaluation (i.e., CT, MRI, electromyography, or other as appropriate), to confirm the diagnosis and to start appropriate treatment.

- At the time of NDA submission, the Integrated Summary of Safety (ISS) noted that the data cut-off date was December 31, 2015, at which point 274 subjects out of planned 380 were enrolled.
- The Sponsor provided an update during the NDA cycle indicating that as of May, 2016, a total of 336 subjects were enrolled.
- Given that study closure was planned for September, 2016, the Sponsor was asked to provide another update on the status of this study and the availability of additional data. The Sponsor verified that enrollment in the study was concluded, with the last patient visit recorded on October 4, 2016. A total of 393 subjects were enrolled and 392 patients were dosed. The Sponsor submitted the finalized complete study report on May 30, 2017.
- In addition to capturing the occurrence of neurological adverse events, the Sponsor was able to capture administration of intraoperative intravenous rescue medications. There were 42 subjects that required intraoperative rescue medications for sedation, analgesia, anxiolysis, or anesthesia. Given the high incidence of rescue, which is directly related to drug efficacy, more information was requested from the Sponsor regarding these particular subjects, including times of intrathecal chloroprocaine administration, time of rescue medications, and surgical procedure duration. The Sponsor was able to provide this information for most of the subjects. Although this study was an observational, open-label safety study, post-hoc efficacy analyses were conducted for the 42 subjects who required rescue to determine the actual rate of failures in this study for those subjects who received 50 mg dose of intrathecal chloroprocaine. Refer to Section 6.1.1 of this review for those details.
- Safety data collected in this study was utilized to increase the total safety database and analyzed in the Safety section of this review (Section 7).

6 Review of Efficacy

Efficacy Summary

Based on the clinical studies submitted in the NDA, chloroprocaine 1% appears to be effective in producing adequate subarachnoid block in patients undergoing surgical procedures < 40 minutes in duration.

Efficacy evaluation was primarily based on the data from the second Phase 2 study (CHL1/02-2014), and the Phase 3 study (CHL1/02-2006/M). The original Phase 2 study (CHL1/02-2004) was not utilized in the formal efficacy analysis because of the

unavailability of the Sponsor to provide original datasets for this study. The Phase 3 study had the largest sample size.

The Sponsor concluded that chloroprocaine 1% has a shorter duration of action when compared to bupivacaine 0.5% isobaric. However, the only approved formulation of bupivacaine in the United States for intrathecal injection is hyperbaric bupivacaine 0.75%, which is also considered the gold standard. In addition, the Phase 3 study was a non-inferiority study design, where the primary efficacy endpoint did not correlate with the ability of intrathecal chloroprocaine injection to provide adequate level of surgical analgesia. Therefore, since the Phase 3 study was conducted using a non-approved product as a comparator arm, and the primary efficacy endpoint did not support drug efficacy, the Sponsor's efficacy conclusions were not clinically relevant.

(b) (4)

50 mg dose is considered appropriately efficacious at this time. (b) (4)

he final conclusion of the efficacy analysis based on all studies submitted is that 50 mg of chloroprocaine 1% is appropriate to provide surgical level of analgesia for surgical procedure that last < 40 minutes. This is also in alignment with the inclusion criteria set forth in all the clinical studies (with the exception of the original Phase 2 study CHL1/02-2004, which had a higher rate of failures), (b) (4)

6.1 Indication

The Sponsor currently proposes the following indication for chloroprocaine 1% injection: CLOROTEKAL® contains chloroprocaine hydrochloride an ester local anesthetic indicated for single intrathecal injection in adults for the production of subarachnoid block (spinal anesthesia).

(Source: NDA 208791 Sponsor's Draft Labeling Text submitted March 17, 2017)

6.1.1 Methods

Three clinical studies were used to support efficacy of chloroprocaine 1%: CHL1/02-2004, CHL1/02-20014, and CHL1/02-2006/M. In addition, some data from Phase 4 safety study, CHL1/01-2006/M was utilized in the efficacy analysis. All of the studies had multiple design features that made evaluation of efficacy difficult to conduct.

(b) (4)

(b) (4) efficacy evaluation of the 50 mg dose of chloroprocaine 1% is the emphasis of this review.

Studies CHL1/02-2004 and CHL1/02-2014:

These were single-site, dose-response, Phase 2 studies that evaluated three doses of chloroprocaine 1% (30 mg, 40 mg, and 50 mg). Neither the primary efficacy endpoint, nor the several secondary efficacy endpoints, utilized in these almost identical studies completely reflected the ability of the surgical block induced by intrathecal chloroprocaine to provide a surgical level of analgesia for the duration of the entire surgical procedure. Study CHL1/02-2014 did have three secondary endpoints that were considered in evaluation of efficacy:

- Time to administration of rescue anesthesia or rescue analgesia (T_{ra})
- Proportion of patients achieving effective anesthesia (see Sponsor's definition in Section 6.5.1)
- Quality of spinal block (see Sponsor's definition in Section 6.5.1)

Upon in-depth review, the Sponsor did not consider administrations of certain intraoperative rescue medications (e.g., midazolam) as rescue, and therefore, the Sponsor's analysis with regard to these secondary endpoints was scrutinized. However, since no subjects needed rescue medications (including midazolam) in the 50 mg cohort (CHL1/02-2014 only), these endpoints were analyzed (see Section 6.1.5). The 30 mg and the 40 mg cohorts were also analyzed.

In addition, post-hoc analyses looking at concomitant medications given in the operating room in order to deduce whether surgical level of analgesia was appropriate were performed. In particular, the following items were evaluated:

- Time of intrathecal chloroprocaine administration
- Surgical start time and surgical end time
- Surgical duration
- Rescue analgesia, anesthesia, or sedation medications
- Time of rescue medication administration

However, not all timepoints of interest were included or available in the original NDA submission. Therefore, the Sponsor was asked to submit all CRFs and operating room records available for each study in order to provide the information necessary for the efficacy analysis. Table 8 below lists the sources of all pertinent data that were used to establish efficacy for this NDA.

Table 8 Sources of Efficacy Data (1% Chloroprocaine: 50mg only)

	Time of Chloroprocaine Injection	Time of Surgery Start	Time of Surgery Finish	Rescue Medications	Time of Rescue Medications
CHL1/02-	CRFs	Estimated	Estimated	CSR	Estimated

2004 (n=15)		by Sponsor from OR records	by Sponsor from OR records		by Sponsor from OR records
CHL1/02- 2014 (n=15)	ADSL dataset	CRFs	CRFs	CM dataset	CM dataset
CHL1/02- 2006/M (n=66)	CM dataset	CRFs	CRFs	CM dataset	Either N/A or estimated by Sponsor from OR records

CRF = Case Report Form; OR = Operating Room; CSR = Clinical Study Report; CM = Concomitant Medications; ADSL = Subject-Level Analysis; N/A = Not Available

Refer to appropriate sections below for more details regarding efficacy analyses for these studies.

Study CHL1/02-2006/M:

This multiple-site, Phase 3 study analyzed the non-inferiority of chloroprocaine 1% (50 mg) versus bupivacaine 0.5% (10 mg) in terms of onset time of sensory block at T10 in minutes. There were numerous design features of this study that made it difficult to evaluate efficacy:

- Non-Inferiority (NI) design
 - The FDA Guidance for Industry *Non-Inferiority Clinical Trials to Establish Effectiveness* warns that since a NI study does not “measure” efficacy of the active control, although such a study may show what appears to be an acceptably small difference between the treatments, due to assay sensitivity, this may or may not support a conclusion that the test drug was effective. In addition, the guidance also states that the usual reason for using an NI active control study design instead of a superiority design is due to an ethical concern, such as “when it would not be ethical to use a placebo, or a no-treatment control, or a very low dose of an active drug, because there is an effective treatment that provides an important benefit (e.g., life-saving or preventing irreversible injury) available to patients for the condition to be studied in the trial.”¹

¹ This guidance is available on the Internet at <http://www.fda.gov/Drugs/default.htm> under Guidances (Drugs). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

- o It is difficult to determine the appropriate margin for a NI study. In a cover letter dated December 22, 2016, the Sponsor wrote “The selection of the non-inferiority margin is based upon a combination of statistical reasoning and clinical judgement [sic]. Statistically, the study was designed following the EMA “Guideline on the choice of the non-inferiority margin”. The study non-inferiority margin (delta) for the primary endpoint (onset time of surgical anesthesia) is 4 minutes. Clinically, when comparing spinal chloroprocaine and bupivacaine, we enrolled patients undergoing elective short-duration surgeries (< 40 min). In this clinical context a difference higher than 4 minutes in readiness to surgery between two different spinal local anesthetics for each patient could translate in the risk of scheduling fewer patients within the same surgical session, therefore becoming clinically relevant.”
 - Since there are a multitude of reasons why a surgical case may stay in the operating room longer than originally booked (e.g., anesthetic induction/block time, availability of surgical equipment, unexpected surgical complications/difficult anatomy, nursing issues, etc.), it is extremely difficult to assert that four minutes difference in readiness for surgery would translate into less patients being booked for a particular surgical block time. Therefore, the rationale presented by the Sponsor for the NI margin is not appropriate.
- Comparator drug
 - o The active comparator drug in this study is isobaric bupivacaine 0.5%, which is not approved in United States for intrathecal administration. The only form of bupivacaine this is approved for intrathecal use in the U.S. is hyperbaric bupivacaine 0.75%. Although isobaric bupivacaine 0.5% is sometimes used off-label in clinical practice via intrathecal route, given the availability of the gold standard product, bupivacaine 0.75%, bupivacaine 0.5% is not an appropriate comparator, particularly in a NI study.
- Primary and secondary endpoints
 - o Neither the primary efficacy endpoint, nor the several secondary efficacy endpoints, reflected the ability of the surgical block induced by intrathecal chloroprocaine (or bupivacaine) to provide a surgical level of analgesia for the duration of the entire surgical procedure. One secondary endpoint, time when subject asks the first time for analgesia (T_{an}) would have been useful, however, upon in-depth review, only time to post-operative analgesia was considered, and thus, this endpoint could not be used to evaluate use of intraoperative rescue medications (i.e., drug efficacy).

Due to the difficulties with the study design described, post-hoc analyses looking at concomitant medications given in the operating room were conducted in order to deduce whether surgical level of analgesia was appropriate. The following items were evaluated:

- Time of intrathecal chloroprocaine administration

- Times of surgical start and surgical end
- Surgical duration
- Rescue analgesia, anesthesia, or sedation medications
- Time of rescue medication administration

Since not all time points above were included in the original NDA submission, Sponsor was asked to submit CRFs for all subjects in this study. Refer to Table 8 above regarding sources of data for this study.

In addition, since the study was conducted at four different centers (See Table 9 below), efficacy results based on post-hoc analyses for both treatment and reference arms were compared between centers. These analyses determined that one clinical site, Marburgo, had substantially more subjects requiring intraoperative rescue medications than the other three sites in both the treatment and reference arms. In particular, increase use of intraoperative rescue midazolam was apparent at Marburgo site, in comparison to the other clinical sites. When asked to provide rationale for this difference in efficacy, the Sponsor responded stating that the possible difference may be attributed to characteristics of subjects treated and to site-specific practice.

Table 9 Number of Subjects Per Study Site (Study CHL1/02-2006/M)

Site Number	Site Name	Number of Subjects	
1	University Hospital of Parma	29	T: 14
			R: 15
2	University Hospital Giessen and Marburg	20	T: 10
			R: 10
3	Regional Hospital of Lugano	77	T: 40
			R: 37
4	Regional Hospital of Mendrisio*	4	T: 2
			R: 2

T = Treatment Arm; R = Reference Arm

* A fourth Centre, belonging to the same premise of the Regional Hospital of Lugano (center 3), managed four patients at the study start. The Principal Investigator is the same of the third center, Dr. Camponovo, Head of Anesthesiology Department. (Source: NDA 208791 Sponsor's Integrated Summary of Effectiveness)

Refer to appropriate sections below for more details regarding efficacy analyses for this study.

Study CHL1/01-2012/M

Although this study was conducted as a post-marketing, observational safety study, information regarding intraoperative rescue medications was collected and reported in the final study report.

A total of 392 subjects were dosed with IT chloroprocaine in the study. Forty-two subjects required intraoperative intravenous medications for sedation, anxiety, analgesia, or anesthesia. On June 1, 2017, the Sponsor was asked to provide a rationale for such a high failure rate (10.7%). Additional information was also requested regarding the timing of rescue medications, surgical procedure durations, list of medicines administered and their indications. On June 9, 2017, the Sponsor responded by providing a list of all subjects who received intraoperative intravenous rescue medications, the names of the medications, and the time of IT chloroprocaine administration in relation to the time of surgical start. The Sponsor also stated that since the study did not limit the type or the amount of medications given for sedation or anxiety in the operating room, the subjects who received medications like propofol or midazolam, were not considered failures. The Sponsor interpreted “failures” as those subjects who received intraoperative medications for indication of analgesia or anesthesia only. These medications were sufentanil, ketamine, metamizole, and paracetamol. Of the forty-two subjects who received intraoperative breakthrough medications, per Sponsor analysis, only thirteen satisfied the criteria for analgesia or anesthesia. One of the thirteen subjects was a puncture failure, and did not receive IT chloroprocaine. Therefore, the Sponsor concluded that only twelve subjects met the “failure criteria,” which is consistent with a clinically-acceptable failure rate of 3%.

The Sponsor’s argument that it is not unusual for patients, with an otherwise satisfactory spinal anesthetic, to require additional anxiety control or sedation in the operating room, even though they are not experiencing surgical pain, is valid. Medications like midazolam and propofol are often given in the operating room to enhance patient comfort and satisfaction, even if the spinal anesthetic is working perfectly. However, there can be clinical scenarios where the spinal anesthetic is not working perfectly, or is incomplete, and patients are given additional anxiety or sedation medications in order to “distract” them from the feeling of pain, without needing to convert to a general anesthetic, especially if the surgical procedure is nearly complete. Since such details are not provided in the study data, it is difficult to conclude whether or not these medications were, in fact, just given for mild sedation or anxiety control, or due to an ineffective surgical block.

Of the forty-two subjects who received intraoperative rescue medications, four were eliminated:

- One subject was not dosed in IT chloroprocaine due to puncture failure
- One subject received only paracetamol, which is often given in the operating room for the indication of post-operative pain control

- Two subjects received only metamizole, which is often given in the operating room for the indication of post-operative pain control

Therefore, if subjects that received propofol, sufentanil, ketamine, or midazolam are considered failures, a total of thirty-eight subjects would be considered as failures for the study. This is a failure rate of 9.7%. However, since these subjects received different doses of IT chloroprocaine, and only the 50 mg dose is being considered for approval at this time, subjects that received a dose of ≥ 50 mg were considered most pertinent. Twenty-three subjects received intraoperative rescue medications that included midazolam, propofol, sufentanil, and ketamine. Subjects who received intraoperative metamizole and paracetamol were not considered. A total of 145 subjects in the study received a dose of IT chloroprocaine that was ≥ 50 mg (Refer to Table 28 for dosing breakdown). In this clinical scenario, the failure rate is 15.9%, which is much higher than what is clinically acceptable. Although it appears to be relatively low, failure rate was not calculated for doses < 50 mg because high failure rates, small sample size, and unreliable rescue medication and surgical duration data in the Phase 2 studies, made formal evaluation of efficacy of these lower doses unwarranted.

The study inclusion criteria included a surgical duration of < 40 minutes. If the rescue medications were given because the surgical time exceeded that time threshold, then the need for intraoperative rescue medications may be appropriate and not considered an efficacy failure, since the spinal anesthetic effect may start to wear off at that point. Since the Sponsor did not provide this data in their response to Information Request received on June 9, 2017, on June 14, 2017, an additional Information Request was sent that inquired whether the Sponsor had data on the time of intraoperative rescue medication. Given that the time of IT chloroprocaine administration was already provided, duration of spinal anesthetic to the time of rescue could then be calculated.

Table 10 Summary of Subjects Who Received 50 mg dose of IT Chloroprocaine and Required Intraoperative Breakthrough for Study CHL1/01-2012/M.

Subject Number	Time of IT CP	Surgery Start	Time of IT CP to Surgery Start (min)	Surgery Duration	Rescue Medication (time)	Time from IT CP Injection to Time of Rescue (min)	Additional Notes
03-003	10:45	11:05	20	N/A	Sufentanil (N/A) Propofol (N/A)	N/A	
03-006	8:30	9:00	30	N/A	Midazolam (N/A)	N/A	
03-008*	8:50	8:50	0	N/A	Propofol	N/A	

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					(N/A)		
03-009	8:50	9:20	30	10	Propofol (9:15)	25	Rescue given prior to surgical start
03-013	9:40	9:45	5	N/A	Propofol (N/A)	N/A	
03-039*	8:45	8:45	0	25	Esketamin (8:45) Propofol (N/A)	0	Rescue given at the same time as CP injection
03-056	11:15	11:40	25	10	Propofol (11:41) Sufentanil (11:41)	26	
03-065	8:20	8:37	17	10	Midazolam (8:19)	-1	Rescue given prior to CP injection
03-068	10:20	10:43	23	30	Midazolam (10:19)	-1	Rescue given prior to CP injection
03-071	9:00	9:25	25	15	Midazolam (8:59)	-1	Rescue given prior to CP injection
03-077*	9:00	9:00	0	20	Sufentanil (9:00) Propofol (9:00)	0	Rescue given at the same time as CP injection
03-079	9:50	10:21	31	19	Midazolam (9:50)	0	Rescue given at the same time as CP injection
03-095*	9:00	9:00	0	25	Sufentanil (8:58) Midazolam (N/A)	-2	Rescue given prior to CP injection (pain in tourniquet site)
04-019	14:21	14:58	37	26	Propofol (14:56)	35	Rescue given prior to surgical start
04-021	12:32	12:54	22	8	Midazolam (12:42)	10	Rescue given prior to surgical start
04-024	9:33	10:11	38	37	Midazolam	14	Rescue given

					(9:47)		prior to surgical start
04-029	12:18	12:45	27	28	Propofol (12:29)	11	Rescue given prior to surgical start
04-034	7:59	8:24	25	32	Propofol (8:21) Sufentanil (8:21)	22	Rescue given prior to surgical start
04-037	8:03	8:28	25	34	Propofol (8:32)	29	
04-052	8:04	8:29	25	26	Propofol (8:14)	10	Rescue given prior to surgical start
04-056	13:40	13:55	15	38	Propofol (13:46)	6	Rescue given prior to surgical start
05-032	15:00	15:20	20	21	Propofol (N/A)	N/A	
05-050	12:50	13:15	25	18	Propofol (N/A) Sufentanil (N/A)	N/A	

IT = Intrathecal; CP = Chloroprocaine; N/A = Not Available

* Per Sponsor-submitted data, time of intrathecal injection and time of surgery start is identical. This clinical scenario is highly unlikely and is most likely erroneous documentation.

(Source: NDA 208791 Sponsor responses to Information Request dated June 9, 2017, and June 28, 2017.)

The Sponsor was not able to provide all documentation requested on surgical duration and time of rescue medication administration for all subjects that required intraoperative rescue medications in the Phase 4 study. Four subjects had documented intrathecal chloroprocaine injection time and surgical start time as identical (Subjects 03-008, 03-039, 03-077, and 03-095). This scenario is highly unlikely, given that surgical block onset is quick, but not instantaneous. In addition, patient positioning and preparation for surgery is not the same as patient positioning and preparation for intrathecal injection, and would therefore, require extra time and effort.

The Sponsor did provide data on time of rescue medication and surgical procedure duration for seventeen subjects of the 23 subjects who required rescue in the ≥ 50 mg dose cohort. Fifteen of them required IV rescue medications either before or during intrathecal chloroprocaine, or prior to the time surgery start:

- One subject received the IV rescue medication prior to intrathecal chloroprocaine injection.
- Three subjects received IV rescue medication at the same time as intrathecal chloroprocaine injection.
- Eleven subjects received IV rescue medication before surgical start time.

Three of the fifteen subjects has surgical start times identical to the intrathecal chloroprocaine injection times, and were therefore were not further analyzed given the likelihood of erroneous information. However, given the other twelve subjects did not require additional intraoperative IV rescue medications, it is reasonable to assume that the medications were given solely to relieve anxiety or to give some sedation prior to surgical start, which is a common and acceptable clinical practice.

The only two subjects that had available data for both IV rescue medications time and surgical start time were subjects 03-056 and 04-037. These subjects required rescue medications 26 and 29 minutes, respectively, after intrathecal chloroprocaine injection.

Nineteen of the twenty three subjects in the ≥ 50 mg dose cohort had data on both time of intrathecal chloroprocaine injection, time of surgical start, and surgical duration. Average time between intrathecal chloroprocaine injection and surgery end (total length of surgical anesthetic required) was calculated to be 44 minutes for these subjects, which is consistent Phase 2 and Phase 3 studies conducted by the Sponsor.

In conclusion, available data on subjects who required rescue medications in study CHL1/01-2012/M is incomplete and has multiple limitations (e.g., possibility of being erroneous in some subjects and unavailable for the lower doses of chloroprocaine). However, the overall evaluation of the data available on subjects in the ≥ 50 mg dose cohort that required rescue medications is supportive of efficacy of 50 mg dose. No other efficacy conclusion could be derived.

6.1.2 Demographics

Tables 11, 12, and 13, provide summarize demographic information for studies CHL1/02-2004, CHL1/02-2014, and CHL1/02-2006/M, respectively. Ethnicity data was not reported in any of the studies.

Table 11 Study CHL1/02-2004 Demographic Data Summary

	30 mg (n=15)	40 mg (n=15)	50 mg (n=15)	P value
Mean Age $\pm$ SD (years)	58.8 $\pm$ 13.0	55.5 $\pm$ 14.1	48.4 $\pm$ 15.9	0.147

Mean Weight ± SD (kg)	81.1 ± 11.9	78.8 ± 12.2	82.1 ± 14.1	0.34
Mean Height ± SD (cm)	171.9 ± 8.4	168.9 ± 7.9	178.5 ± 12.8	0.68
ASA Physical Status (I/II)	4/11	2/13	4/11	0.59
Sex (Male/Female)	6/9	7/8	8/7	0.76

ASA = American Society of Anesthesiologists

(Source: NDA 208791 Sponsor's Clinical Study Report for Study CHL1/02-2004)

Table 12 Study CHL1/02-2014 Demographic Data Summary

Demographic data	FAS, PK and safety set - N=45		
Dose group	30 mg	40 mg	50 mg
Gender			
Female – n (%)	6 (40%)	6 (40%)	6 (40%)
Male – n (%)	9 (60%)	9 (60%)	9 (60%)
Age (years)			
Mean ± SD	40.8±12.1	39.4±12.5	41.5±13.9
Median (range)	42 (25-58)	41 (19-58)	40 (20-63)
BW (kg)			
Mean ± SD	73.27±14.11	70.27±13.32	74.07±13.14
Range	78 (47-99)	66 (52-99)	73 (48-98)
Height (cm)			
Mean ± SD	172.0±6.9	170.2±9.3	168.9±7.1
Median (range)	170 (158-185)	173 (153-185)	170 (153-180)
BMI (kg/m²)			
Mean ± SD	24.65±3.96	24.19±3.62	25.87±3.71
Median (range)	25.30 (18.8-30.6)	22.20 (19.0–30.6)	25.80 (18.3-31.3)
Race			
Mestizo – n (%)	1 (6.7%)	1 (6.7%)	0
White – n (%)	14 (93.3%)	14 (93.3%)	15 (100%)

FAS = Full Analysis Set; PK = Pharmacokinetic; SD = Standard Deviation

(Source: NDA 208791 Sponsor's revised Integrated Summary of Effectiveness)

Table 13 Study CHL1/02-2006/M Demographic Data Summary

	Chloroprocaine Group (n=66)	Bupivacaine Group (n=64)
Mean Age ± SD (years)	45.2 ± 15.9	50.6 ± 15.2
Mean Weight ± SD (kg)	71.4 ± 11.9	77.1 ± 12.1
Mean Height ± SD (cm)	168.4 ± 7.2	172.4 ± 8.8
BMI ± SD	25.1 ± 3.8	25.9 ± 3.3

ASA Physical Status (I/II)	33/33	26/38
Sex (Male/Female)*	42/24	27/37

SD = Standard Deviation; ASA = American Society of Anesthesiologists

*Difference between groups is statistically significant (P-value 0.0143)

(Source: NDA 208791 Sponsor's Clinical Study Report for Study CHL1/02-2006/M)

The only demographic parameter in study CHL1/02-2006/M that met statistical significance between the study groups was sex. Chloroprocaine group had significantly higher male to female ratio than the bupivacaine group.

Table 14 Study CHL1/02-2014 Subject Age Distribution

	Chloroprocaine 1% - 30 mg		Chloroprocaine 1% - 40 mg		Chloroprocaine 1% - 50 mg			
Age (years)	Count	Column %	Count	Column %	Count	Column %	Total Count	% of Total
≤ 39	7	46.7	6	40.0	7	46.7	20	44.44
40 to 64	8	53.3	9	60.0	8	53.3	25	55.56
Total	15	100.0	15	100.0	15	100.0	45	100.00

It is of note that no subject in Study CHL1/02-2014 was over the age of 65.

More detailed age distribution for Study CHL1/02-2006/M is shown in Table 15 below.

Table 15 Study CHL1/02-2006/M Subject Age Distribution

	Bupivacaine 0.5% (10 mg)		Chloroprocaine 1% (50 mg)			
Age (years)	Count	Column %	Count	Column %	Total Count	% of Total
≤ 39	17	26.6	26	39.4	43	33.08
40 - 64	30	46.9	33	50.0	63	48.46
≥ 65	17	26.6	7	10.6	24	18.46
Total	64	100.0	66	100.0	130	100.00

Half of the subjects in the chloroprocaine arm were between 40 and 64 years old. The age group least represented was the greater than 65-year-olds, with only 10% of subjects.

The table below represents demographic data from Study CHL1/01-2012/M.

Table 16 Summary of Demographic Characteristics at Study Entry (CHL1/01-2012/M)

	All(N=393)	<65y(N=306)	>65y(N=87)
	N	N	N
Age (years)	51.5±15.4	46.0±12.7	70.8±4.7
Sex (male)	235 (59.8)	189 (61.8)	46 (52.9)
Race (Caucasian)	388 (98.7)	301 (98.4)	87 (100)
Height (cm)	173±9.9	174±9.7	168±9.2
Weight (kg)	81.8±16	82.7±16.1	78.6±15.3
BMI	27.4±5	27.3±5.1	27.8±4.8

(Source: NDA 208791 Sponsor's Final Study Report for Study CHL1/01-2012/M)

All subjects in Study CHL1/01-2012/M were classified as ASA I or II. Most patients were less than 65 years old and approximately 60% were males.

6.1.3 Subject Disposition

With a single administration of study drug in a confined setting such as the operating room, it would be expected that most subjects treated would complete the study. This was the case for all the clinical studies in this NDA submission.

Study CHL1/02-2004:

One subject (Subject 45) was discontinued from the study. This subject withdrew the informed consent prior to placement of spinal. This subject was originally randomized to receive 30 mg of chloroprocaine.

Study CHL1/02-2014:

One subject (Subject 29) discontinued the study before placement of spinal due to non-compliance with injection. This subject was originally randomized to receive 30 mg of chloroprocaine.

Study CHL1/02-2006/M:

Out of the 130 randomized subjects, 9 were excluded from the Per Protocol (PP) set due to incomplete anesthesia or non-achievement of the anesthesia level required by the protocol. The following subjects were discontinued:

- Treatment arm:
 - o Subject 203 – Sensory block only to L1, required intraoperative anxiolytic medication
 - o Subject 205 – Treatment failure, required general anesthesia
- Reference arm:

- o Subject 104 – Sensory block to T10 not achieved (however was able to undergo surgery without supplemental analgesics/anesthetics)
- o Subject 107 – Treatment failure, required general anesthesia
- o Subject 111 – Sensory block to T10 not achieved (however was able to undergo surgery without supplemental analgesics/anesthetics)
- o Subject 204 – Treatment failure, required general anesthesia
- o Subject 210 – Treatment failure, required general anesthesia
- o Subject 220 – Loss of pinprick at T10 not achieved, required supplemental analgesia, sedation
- o Subject 304 – Spinal did not achieve surgical level; required supplemental analgesia, sedation

Study CHL1/01-2012/M:

Out of 393 subjects enrolled in the study. Six subjects did not complete the study:

- Subject 03-076 – discontinued due to an adverse event (unable to access spinal space due to anatomical reasons, and therefore, did not receive IT chloroprocaine)
- Subjects 05-009, 05-017, 05-024, and 05-037 – lost to follow-up
- Subject 04-002 – had “serious alterations of cardiac conduction” and therefore, did not receive the study drug.

6.1.4 Analysis of Primary Endpoint(s)

Study CHL1/02-2004

- Primary endpoint:
 - o Comparison of the efficacy of the three chloroprocaine dosages (30 mg chloroprocaine isobaric 1%; 40 mg chloroprocaine isobaric 1%; 50 mg chloroprocaine isobaric 1%) in terms of time of complete regression of spinal block (T_{ea}) and achievement of home discharge criteria (T_{hd}).
- Although complete regression of spinal block implies that a spinal block was accomplished, it does not imply that the spinal block provided adequate surgical analgesia for the surgical procedure. Given that this primary endpoint would not inform efficacy of the drug, analysis of this primary endpoint was not performed.

Study CHL1/02-2014

- This study had nearly identical study design and procedures, and similar primary and secondary endpoints as study CHL1/02-2004, with the exception of pharmacokinetic endpoints, which were lacking in study CHL1/02-2004.
- Primary endpoint:
 - o To evaluate the efficacy of the three chloroprocaine HCl 1% doses (30 mg; 40 mg; 50 mg) in terms of time to complete regression of spinal block (T_{ea}).

- Although complete regression of spinal block implies that a spinal block was accomplished, it does not imply that the spinal block provided adequate surgical analgesia for the surgical procedure. Given that this primary endpoint would not inform efficacy of the drug, analysis of this primary endpoint was not performed.

Study CHL1/02-2006/M

- Primary endpoint:
 - The non-inferiority of chloroprocaine 1% (50 mg) versus bupivacaine 0.5% (10 mg) in terms of onset time of sensory block at T10 (assessed by the loss of pin-prick sensation) in minutes. Non-inferiority margin was set to 4 minutes.
- Although onset time of sensory block at T10 implies that a spinal block was accomplished, it does not imply that the spinal block provided adequate surgical analgesia for the surgical procedure. Spinal blocks can fail to provide adequate surgical level of analgesia even though the sensory level (tested via pin-prick sensation) appears adequate for multiple reasons (e.g., patchy block). Given that this primary endpoint would not necessarily inform efficacy of the drug to provide a surgical level of analgesia, analysis of this primary endpoint was not performed.

Study CHL1/01-2012/M:

Since this study was designed primarily as a safety study, refer to Section 7.1.1 below for discussion of primary endpoints.

6.1.5 Analysis of Secondary Endpoints(s)

Study CHL1/02-2004

- Secondary endpoints:
 - To investigate the efficacy of the three chloroprocaine dosages (as stated above) based on
 - Time to onset to motor block (T_{mb})
 - Time from the end of the spinal injection to readiness of surgery ($T_{sp}-T_{ss}$)
 - Resolution of motor block or time to unassisted ambulation ($T_{mb=0}$)
 - Time of offset of sensory block (T_{ea})
 - Maximum level of sensory block (T_{mbMAX})
 - Time to void (T_{uv})
 - Time to eligibility for home discharge (T_{hd})
- As with the primary endpoint, none of the secondary endpoints listed here reflect the ability of the surgical block performed to provide adequate surgical level of analgesia that lasts the entire duration of the surgical procedure. Since these secondary endpoints do not inform drug efficacy, they were not analyzed for the purpose of this NDA review.

Study CHL1/02-2014

- Secondary endpoint:
 - o To evaluate the efficacy of three chloroprocaine HCl 1% doses in terms of
 - Time to onset of sensory block (T_{sb})
 - Time to onset of motor block (T_{mb}),
 - Time to readiness for surgery (T_{rs})
 - Time to resolution of motor block
 - Time to unassisted ambulation (T_{ua})
 - Time to resolution of sensory block to S1 (T_{S1})
 - Sensory block metamer levels during the block
 - Maximum level of sensory block (SB_{max})
 - Time to maximum level of sensory block (T_{sbmax})
 - Time to regression of two dermatomers with respect to the maximum level of sensory block (T_{rd})
 - Time to first spontaneous urine voiding (T_{uv})
 - Time to administration of rescue anesthesia or rescue analgesia (T_{ra})
 - Time to first post-operative analgesia (T_{pa})
 - Time to eligibility for home discharge (T_{hd})
 - Proportion of patients achieving effective anesthesia
 - Effective anesthesia was defined as the presence of adequate sensory and motor blocks with adequate duration to cover surgery
 - Quality of spinal block
 - The quality of spinal block was verified according to the need for supplementary intravenous analgesics and sedation as follows:
 - o Adequate spinal block = neither sedation nor analgesics required to complete surgery
 - o Inadequate spinal block = additional anesthesia or analgesia required to complete surgery
 - o Failed spinal block = general anesthesia required to complete surgery
 - o To assess the concentration of chloroprocaine and its metabolite 2-chloro-4-aminobenzoic acid (CABA) in plasma after administration of each dose
 - o To assess the excretion of the CABA in urine (as % of the administered dose)
- Although the Sponsor did not consider midazolam as a rescue medication when given intraoperatively, none of the subjects in the 50 mg cohort required intraoperative rescue medications, including midazolam. Therefore, the secondary endpoints of time to administration of rescue anesthesia or rescue analgesia (T_{ra}), proportion of patients achieving effective anesthesia, and quality of spinal block were analyzed. Statistical analysis performed by statistical reviewer, Yan Zhou, Ph.D., confirmed all three endpoints.

- Per Sponsor's analysis, the proportion of patients reaching an effective anesthesia and an adequate spinal block was 100% in the 50 mg cohort. No subject in the 50 mg dose cohort required rescue medications.

Study CHL1/02-2006/M

- Secondary endpoints:
 - o Time to onset of sensory block (T_{sb})
 - o Time to onset of motor block assessed by using the modified Bromage's scale (T_{mb})
 - o Maximum level of sensory block (T_{sbmax})
 - o Resolution (offset) of sensory block to S1 (T_{S1}) (reported, on CRFs, as time to end of anesthesia)
 - o Resolution of motor block (Bromage score = 0) ($T_{mb=0}$)
 - o Time to unassisted ambulation (T_{uv})
 - o Presence or not of urinary retention
 - o Time when subject asks the first time for analgesia (T_{an})
 - Only evaluated time for first post-operative analgesic
 - o Time to eligibility for home discharge (T_{hd}) (for day surgery only)
- As with the primary endpoint, none of the secondary endpoints listed here reflect the ability of the surgical block performed to provide adequate surgical level of analgesia that lasts the entire duration of the surgical procedure. Since these secondary endpoints do not inform drug efficacy, they were not analyzed for the purpose of this NDA review.

6.1.6 Other Endpoints

Due to the inability to use all of the primary endpoints and most of the secondary endpoints that were selected by the Sponsor for each study in order to properly evaluate efficacy, post-hoc analyses were performed which focused on evaluating the use of intraoperative rescue medications for analgesia, anxiety, sedation, or anesthesia for all dose cohorts. The following time points that were analyzed (when available):

- Intrathecal (IT) chloroprocaine administration
- Surgical start and end
- Surgery duration
- Intraoperative rescue medications

Table 17 below summarizes the number of subjects in the 50 mg dose cohort that needed intraoperative rescue medications for all three studies. The lower dose cohorts are summarized in Tables 19 and 20.

Table 17 Number of Subjects Requiring Rescue Medications in the 50 mg Cohort

Dose Cohort (mg)	CHL1/02-2004 N=15 (%)	CHL1/02-2014 N=15 (%)	CHL1/02-2006/M N=66 (%)	TOTAL N=96 (%)
50	2* (13)	0 (0)	6** (10)	8 (8)

* Unclear whether all data is available because Sponsor lacks original datasets

** Incidence may be less, however data missing on time of rescue

Study CHL1/02-2004

Although the Sponsor was not able to provide original data for this study, translated CRFs and OR records were submitted. The OR records were not legible and were not reviewed. However, the Sponsor was able to analyze the OR records and the CRFs for pertinent time points related to intraoperative rescue medications.

Table 18 Study CHL1/02-2004 Failures: 50 mg Cohort (N=15)

Subject	Time of IT CHL	Surgical Duration (min) (+/- 15 min)	Medication(s) (time) (+/- 15 min)	Indication	Other Pertinent Information
024	11:59	20	Fentanyl (12:20; 13:00) Midazolam (13:00)	Intraoperative analgesia Intraoperative sedation	Start of surgery 60 min after IT injection
040	8:43	N/A	Fentanyl (9:43)	Intraoperative analgesia	

IT = Intrathecal; CHL = Chloroprocaine; N/A = Not Available

The Sponsor estimated that the average duration of action of a single intrathecal 50 mg dose of chloroprocaine 1% is 100 minutes. Although the surgical procedure did not start until sixty minutes after intrathecal chloroprocaine injection for subject 024, the first dose of fentanyl was administered approximately (+/- 15 minutes) twenty-one minutes after the intrathecal chloroprocaine, and the second dose of fentanyl plus midazolam

were administered approximately (+/- 15 minutes) sixty-one minutes after the intrathecal chloroprocaine. Even with allotment of additional fifteen minutes (since times of administration of rescues are crudely estimated by Sponsor), this subject still required rescue within 76 minutes for intrathecal chloroprocaine, which is well below the proposed duration of action. Therefore, Subject 024 is considered a failure.

Limited information was provided for Subject 040, however, rescue fentanyl was administered sixty minutes after intrathecal chloroprocaine, and therefore, this subject can also be classified as a failure.

Regarding the overall surgical duration, only mean duration data are available from the CRFs and the study report. Mean duration was estimated by the Sponsor to be 45 ± 15 minutes in group treated with 30 mg, 50 ± 13 minutes in group treated with 40 mg, and 48 ± 15 minutes in group treated with 50 mg. The Sponsor also provided data on "time to readiness for surgery." However, these data do not represent time from intrathecal injection to the time of surgical incision, but rather time from intrathecal injection to time of "block onset" evaluated by the Sponsor.

In the proposed labeling,



The table below summarizes the failures in the lower dose cohorts.

Table 19 Study CHL1/02-2004 Failures: 30 mg and 40 mg Cohorts (N=29)

Subject	Dose (mg)	Time of IT CHL	Surgical Duration (min) (+/-15min)	Medication (s) (+/-15min)	Indication
012	30	12:45	40	Fentanyl (13:30)	Intraoperative analgesia

020	30	9:47	25	Fentanyl	Intraoperative analgesia
026	30	10:08	N/A	Fentanyl (10:30)	Intraoperative analgesia
029	30	8:48	50	Fentanyl (9:15)	Intraoperative analgesia
033	30	8:47	60	Fentanyl (10:00)	Intraoperative analgesia
035	30	10:12	105	Fentanyl (11:00)	Intraoperative analgesia
036	30	17:41	N/A	Fentanyl	Intraoperative analgesia
010	40	10:58	N/A	Midazolam (11:15)	Intraoperative anxiety
019	40	8:29	15	Fentanyl	Intraoperative analgesia
022	40	12:54	30	Fentanyl (13:30)	Intraoperative analgesia
027	40	10:54	N/A	Fentanyl (11:50)	Intraoperative analgesia
030	40	12:07	N/A	Fentanyl (12:45)	Intraoperative analgesia
32	40	12:52	40	Fentanyl (13:45)	Intraoperative analgesia

IT = Intrathecal; CHL = Chloroprocaine; N/A = Not Available

In comparison to the 50 mg dose cohort, the lower dose cohorts each had significantly higher number of failures. There were seven failures in the 30 mg cohort and six failures in the 40 mg cohort. All but one subject required intraoperative fentanyl, which is highly suspicious for having an insufficient or incomplete surgical block. The lengths

of surgical procedures ranged from 15 – 105 minutes. However, the Sponsor was not able to provide this information for all of the subjects. The time from intrathecal chloroprocaine injection to the time of rescue ranged from 17 – 73 minutes. Mean time to rescue was not calculated due to several patients having missing time points. Given the high failure rate in the 30 mg and the 40 mg dose cohorts, the small sample size, and incomplete data for subject failures, (b) (4)

CHL1/02-2014

No subjects required intraoperative rescue medications for analgesia, anxiety, sedation, or anesthesia in the 50 mg dose cohort.

The average surgical procedure duration in this study for all dose groups was only 22 minutes (range 5-74 minutes). Patient whose surgical procedure lasted 74 minutes was in the 30 mg chloroprocaine group and required breakthrough fentanyl during the procedure. The average time from intrathecal injection to surgical incision was 21 minutes for all dose groups (range 13-42 minutes). This time is relevant because it is not uncommon for the surgical preparation to take a significant amount of time, prior to actual surgical incision. The longest recorded surgical procedure was 74 minutes and the second longest was 42 minutes. If you add the average time from intrathecal injection to surgical incision (21 minutes) and the average length of surgery (22 minutes) in this study, only a total of 43 minutes of chloroprocaine effect is demonstrated. (b) (4)

Table 20 Study CHL1/02-2014 Failures: 30 mg and 40 mg Cohorts (N=30)

Subject	Dose (mg)	Time of IT 1% CHL	Surgery End	Surgery Duration (min)	Rescue Medication(s) (time)	Time from IT CHL to Rescue (min)	Indication
005	30	13:04	14:08	42	Fentanest (13:37) Midazolam (13:28) propofol (13:57)	33 24 53	Rescue anesthesia, rescue sedation, rescue anesthesia
016	30	11:19	11:55	20	Fentanest (11:45) Midazolam (N/A)	26 N/A	Rescue analgesia

036	30	10:47	12:23	74	Fentanest (11:57)	70	Intraoperative analgesia
012	40	8:22	9:00	15	Fentanest (8:39) Midazolam (8:39)	17 17	Rescue analgesia, sedation
019	40	11:45	12:30	9	Midazolam (12:23)	38	Sedation
038	40	12:11	13:00	30	Fentanest (12:32) Midazolam (12:32)	21 21	Rescue analgesia, sedation

IT = Intrathecal; CHL = Chloroprocaine; N/A = Not Available

In comparison to the 50 mg dose cohort, which had no failures, each of the lower dose cohorts had three subject failures. All but one subject required intraoperative fentanyl with or without midazolam or propofol, which is highly suspicious for having an insufficient or incomplete surgical block. The lengths of surgical procedures ranged from 9 – 74 minutes. The time from intrathecal chloroprocaine injection to the time of rescue ranged from 21 – 70 minutes. Mean time to rescue for fentanyl only was 33 minutes. Given the high failure rate in the 30 mg and the 40 mg dose cohorts (in both Phase 2 studies), the small sample size, and incomplete data for subject failures, (b) (4)

CHL1/02-2006/M

The Sponsor submitted OR records, which were illegible, and CRFs (in English) for this study, since the original dataset did not contain time of rescue medication administration. The Sponsor was asked to examine the OR records and CRFs and provide time or estimate the time of rescue medication for all subjects enrolled in the study, if possible. The Sponsor was only able to establish times of rescue for two subjects in the treatment arm and four subjects in the reference arm. Tables 21 and 23 below represent treatment failures in the treatment arm and the reference arm, respectively.

Table 21 CHL1/01-2006/M Failures Treatment (1% Chloroprocaine) Arm (N=66)

Subject	Time of IT 1% CHL	Surgery Start	Surgery End	Surgery Duration	Rescue Medication(s) (time)	Indication	Study Site	Other Pertinent Information
203	8:06	8:21	8:47	26	Midazolam (N/A)	Intraoperative anxiety	M	Sensory level to L1 only Subject discontinued
205	8:11	8:35	9:05	30	Propofol, Sevoflurane, Sufentanil (all at 8:34)	Intubation	M	Subject discontinued
211	7:56	8:20	8:55	35	Midazolam (N/A)	Intraoperative anxiety	M	
202	13:30	14:12	15:00	48	Midazolam (N/A)	Intraoperative anxiety	M	
212	7:51	8:13	9:15	62	Midazolam (N/A)	Intraoperative anxiety	M	
121	13:34	13:42	15:00	78	Fentanyl (14:30)	Sedation	P	

IT = Intrathecal; CHL = Chloroprocaine; M = Marburg; P = Parma; N/A = Not Available

Only six subjects (out of 66) required rescue medications in the treatment arm. The Sponsor was not able to provide time of intraoperative rescue medication administration for Subjects 203, 211, 202, and 212. However, the data in Table 21 below demonstrate that the range of time intervals between intrathecal chloroprocaine injection to surgery end was 41 – 90 minutes, (b) (4)

Therefore, regardless of the missing data on time of all rescue medication administration, all subjects listed can be classified as treatment failures.

Table 22 CHL1/01-2006/M Failures Treatment (1% Chloroprocaine) Arm: Time to Surgery End Versus Time to Rescue

Subject	Time from IT CHL Injection to Surgery End (min)	Time from IT CHL Injection to Rescue Medication Administration (min)
203	41	N/A
205	54	23
211	59	N/A
202	90	N/A
212	84	N/A

121	86	56
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IT = Intrathecal; CHL = Chloroprocaine; N/A = Not Available

In addition to time of surgery and time of rescue medications, study site analysis for all treatment failures determined that five out of six treatment failures occurred at Marburgo clinical site (See Table 21 above). When asked to provide a rationale for this apparent difference in efficacy, the Sponsor stated that possible differences seen in the amount of rescue medications required at Marburgo site versus the other three study sites may be attributed to characteristics of subjects treated at Marburgo and to site-specific practice. Inspection report from the Office of Scientific Investigations is still pending. One study site (Mendrisio) was not inspected because it enrolled only four subjects.

Although the chosen reference arm (bupivacaine 0.5%) does not represent an ideal comparator since the product is not currently approved for intrathecal administration in the United States, the same analyses were performed in the reference arm in order to detect whether a similar pattern of failure rates, and particularly failure rates at each study site, were present in this arm.

Table 23 CHL1/01-2006/M Failures Reference (0.5% Bupivacaine) Arm (N=64)

Subject	Time of IT 1% CHL	Surgery Start	Surgery End	Surgery Duration	Rescue Medication(s) (time)	Indication	Study Site	Other Pertinent Information
107	8:10	N/A	N/A	N/A	N/A	General anesthesia	P	No CRF filled out Subject discontinued
204	12:20	12:41	13:25	44	Fentanyl, Pentolax, Propofol (12:40*)	Intubation	M	No motor or sensory block achieved Subject discontinued
206	7:54	8:16	8:47	31	Midazolam (N/A)	Intraoperative sedation	M	
210	14:01	14:30	14:59	29	Fentanyl, Propofol, Suprane (all at 14:21) Midazolam (N/A)	Intubation	M	No level of block achieved after 20 minutes Subject

								discontinued
220	13:35	14:05	14:19	14	Fentanyl, Ketanest, Propofol (all at 14:05)	Pain and sedation	M	Loss of pinprick at T10 not achieved Subject discontinued
304	12:59	13:45	14:05	20	Propofol, Rapifen, Sintenyil (all at 13:24)	Pain, anesthesia induction	L	Block did not achieve level at T10 after 25 minutes Subject discontinued

IT = Intrathecal; CHL = Chloroprocaine; CRF = Case Report Form; M = Marburgo; P = Parma; L = Lugano; N/A = Not Available
 * Estimated by Sponsor (+/- 15 minutes)

The table above demonstrates that there were six treatment failures in the reference arm. Although not all time of rescue medication administration was available, the range of time intervals between intrathecal bupivacaine injection to surgery end was 44 – 66 minutes (see Table 24 below). Applying the same criteria as for chloroprocaine in identifying treatment failures, or considering the expected (longer) duration of action of bupivacaine, yields the same conclusion: all six subjects can be classified as treatment failures.

Table 24 CHL1/01-2006/M Failures Reference (0.5% Bupivacaine) Arm: Time to Surgery End versus Time to Rescue

Subject	Time from IT CHL Injection to Surgery End (min)	Time from IT CHL Injection to Rescue Medication Administration (min)
107	N/A	N/A
204	65	20*
206	53	N/A
210	58	20
220	44	30
304	66	25

IT = Intrathecal; CHL = Chloroprocaine; N/A = Not Available
 * Estimated by Sponsor (+/- 15 minutes)

Additional analysis of treatment failures in the reference arm by study site revealed that four out of the six subjects were treated at the Marburgo clinical site. This finding supports the rationale that site-specific practice (e.g., procedural and overall anesthetic

management of practitioners at that site) may be cause of the discrepancy seen with the amount of failures at Marburgo (pending inspection results).

The average surgery duration for all subjects in the chloroprocaine arm in this study was 23 minutes (range 3 – 78 minutes). The average time from intrathecal chloroprocaine injection to surgical incision was 16 minutes (range 3-42 minutes). Only one other subject in the study had a surgical procedure that lasted over 60 minutes (Subject 212 had a procedure that lasted 62 minutes). Neither subject who had procedures last over 60 minutes required breakthrough medications. However, the average time from intrathecal injection to surgical end was 39 minutes. (b) (4)

6.1.7 Subpopulations

The data from pooled analyses across all three studies used to support efficacy indicate that the dosing recommendations based on dose-response relationship is unchanged in all subpopulations evaluated.

In general, uptake and spread of local anesthetics after intrathecal injection are determined by several factors, including dose, volume of injectate, baricity of the drug, and patient positioning. Patient-specific factors that may affect distribution of the local anesthetic in the intrathecal space are intra-abdominal pressure, anatomic configuration of the spinal canal, and cerebral spinal fluid (CSF) volume. (Hocking & Wildsmith, 2004) In addition, rare genetic abnormalities (Sheets, 2006) such as the N395K mutation (mutation of a sodium channel that attenuates the inhibitory effects of local anesthetic drugs) may change the efficacy profile of a local anesthetic.

Tables 25 and 26 below demonstrate the study population of Study CHL1/02-2006/M by sex and race, respectively. In the chloroprocaine arm, there were significantly more females enrolled than males. The majority of the study population (95%) was white, with over 92% subjects being white in the chloroprocaine arm.

Table 25 Study CHL1/02-2006/M Subject Population by Sex

	Bupivacaine 0.5% (10 mg)		Chloroprocaine 1% (50 mg)			
Sex	Count	Column %	Count	Column %	Total Count	% of Total
F	27	42.2	42	63.6	69	53.08
M	37	57.8	24	36.4	61	46.92
All	64	100.0	66	100.0	130	100.00

F = Female; M = Male

Table 26 Study CHL1/02-2006/M Subject Population by Race

	Bupivacaine 0.5% (10 mg)		Chloroprocaine 1% (50 mg)			
Race	Count	Column %	Count	Column %	Total Count	% of Total
Asian	1	1.6	3	4.5	4	3.08
Black or African American	0	0.0	2	3.0	2	1.54
White	63	98.4	61	92.4	124	95.38
All	64	100.0	66	100.0	130	100.00

Table 27 Study CHL1/02-2006/M Treatment Failures Demographics

Subject	Arm	Age (years)	Sex	Race	BMI	Height (cm)
203	C	18	F	Asian	20.3	166
205	C	72	F	White	27.5	165
211	C	56	F	White	31.8	170
202	C	53	M	White	25.8	175
212	C	45	M	White	29.3	180
121	C	64	M	White	23.0	178
107*	B	N/A	N/A	N/A	N/A	N/A
204	B	57	F	White	23.1	157
206	B	54	M	White	27.4	176
210	B	43	F	White	22.2	171
220	B	42	F	White	22.5	170
304	B	60	M	White	27.7	171

N/A = Not Available; C = Chloroprocaine; B = Bupivacaine; F = Female; M = Male; BMI = Body Mass Index

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

Table 27 above lists the demographic characteristics of treatment failures in study CHL1/02-2006/M. Age, BMI, and height in the treatment failures were mostly within the average range calculated for the entire study subject population (see Section 6.1.2 Demographics). There was one subject failure over the age of sixty-five (24 subjects ≥ 65 were enrolled in the study). Subject failures were evenly distributed between males

and females. All the treatment failures, except for one, were white, which was also expected given that over 95% of the study population was white. Overall, this data does not suggest differences in efficacy of chloroprocaine based on age, sex, race, BMI, and height. Ethnicity data was not recorded in the study, and therefore not evaluated.

There were no subject failures in the 50 mg chloroprocaine arm of Study CHL1/02-2014. However, Table 28 summarizes demographic characteristics of subject failures in the 30 mg and the 40 mg chloroprocaine arms.

Table 28 Study CHL1/02-2014 Demographic Characteristics of Subject Failures

Subject	Chloroprocaine Dose (mg)	Age (years)	Sex	Race	BMI	Height (cm)
012	40	41	M	White	20.7	173
019	40	19	F	White	22.1	170
038	40	41	F	White	27.5	155
005	30	25	M	White	30.6	180
016	30	33	F	White	20.1	180
036	30	57	M	White	27	170

M = Male; F = Female; BMI = Body Mass Index

General demographic data for each dose cohort in Study CHL1/02-2014 can be located in Section 6.1.2 Demographics. When the demographic data above is compared to the overall study demographic data, no definitive conclusions can be drawn regarding efficacy of intrathecal chloroprocaine based on subject age, sex, race, BMI, or height. Ethnicity data was not recorded in the study, and therefore not evaluated.

(b) (4)

It should be noted that the safety and efficacy of intrathecal chloroprocaine has not been evaluated in pediatric patients at this point in time.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

(b) (4)

Based on the pivotal studies submitted in this NDA, the Sponsor provided sufficient evidence to support the 50 mg dose of intrathecal chloroprocaine.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Based on the mechanism of action of chloroprocaine and its acute administration, there is no concern for its persistence of efficacy or tolerance to its effects. Section 6.1.7 discusses the theoretical possibility of persistence of efficacy in patients with known pseudocholinesterase deficiency. However, available data in literature demonstrate that such differences in efficacy would be likely be minimal. (Kambam, 1989)

6.1.10 Additional Efficacy Issues/Analyses

One possible genetic factor, which was not studied by the Sponsor, pseudocholinesterase deficiency may theoretically impact the efficacy of chloroprocaine in the cerebrospinal space because the main clearance mechanism of chloroprocaine is via hydrolysis by pseudocholinesterase. However, Kambam, et. al., analyzed cerebrospinal fluid (CSF) for pseudocholinesterase (PCHE) activity. His group discovered that CSF has low PCHE activity and concluded that “The PCHE activity that is present in CSF is probably clinically insignificant for the metabolism of ester type of local anesthetics in CSF.” (Kambam, 1989)

Primary inherited erythromelalgia (IEM) is another rare genetic condition may impact the efficacy of chloroprocaine in the spinal space. In particular, mutation known as N395K, located on the S6 segment of domain I, is associated with a very serious form of IEM. This mutation is located on the gene segment which is responsible for the transcription of the locus which binds local anesthetic. It is theorized that this directly affects the interaction of local anesthetic with the channel by reducing their sensitivity to the local anesthetic. One study demonstrated that in the case of patients with IEM, lidocaine relieves pain in only 55% of cases (Markovic, 2015). Therefore, it is possible that patients with the diagnosis of IEM may have decreased efficacy of intrathecal chloroprocaine, however, it appears that no clinical data is available to support this hypothesis.

7 Review of Safety

Safety Summary

Chloroprocaine (first approved in the U.S. in 1955) is currently approved for subcutaneous injection, peripheral nerve block, and epidural/caudal administration. Since the introduction of preservative-free formulations for epidural administration, there has been limited safety concerns regarding its administration published in literature. Chloroprocaine is typically used in the obstetric patient population, with no additional safety concerns identified in literature.

The Sponsor utilized data from four clinical studies (two Phase 2 studies, one Phase 3 study, and one Phase 4 study) to demonstrate safety of their intrathecal chloroprocaine 1%. In addition, the Sponsor submitted European postmarketing data, as well as, literature data to support their product.

No deaths or serious adverse events were reported in the chloroprocaine arms in the clinical studies conducted by the Sponsor. A total of 130 TEAEs were reported for Phase 2, 3 and 4 studies. The most frequently-occurring adverse events across all studies, case reports, and literature were hypotension, bradycardia, headache, and nausea. These adverse events are well-described in literature in association with spinal anesthesia, and seemingly do not appear more frequently with chloroprocaine than with other local anesthetics administered intrathecally (most notably, lidocaine and bupivacaine).

The neurological adverse events of interest with spinal anesthetics are CES and TNS because of their severity and possibility of prolonged duration and neurological deficits. The Sponsor's postmarketing Phase 4 study (CHL1/01-2012/M) was dedicated to evaluate the incidence of these events. Three hundred ninety-two subjects were dosed in this study and only one subject possibly experienced symptoms indicative of TNS. Sponsor did include several reports from the European postmarketing data and literature that described possible CES and TNS cases associated with intrathecal chloroprocaine (cases discussed in detail in appropriate sections below). However, given the totality of the data presented, the infrequency of these cases, and the multiple confounders associated with them, at this time there does not appear to be a disproportionately high incidence of neurologic complications with chloroprocaine that would preclude approval or warrant additional post-approval studies.

7.1 Methods

The original NDA submission consisted of two clinical studies performed by the Sponsor, one Phase 2 study (CHL1/02-2014) and one Phase 3 study (CHL1/02-2006/M). In addition, the original NDA submission contained postmarketing individual case safety reports (ICSRs) summary and some partial data collected for Phase 4 post-authorization safety study (CHL1/01-2012/M), which was not completed at the time of the NDA submission.

During the review cycle, the Sponsor was asked to submit an additional previously-conducted Phase 2 study (CHL1/02-2004), as well as the final study report for study CHL1/01-2012/M.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

CHL1/02-2004:

- Safety endpoints:
 - o To investigate the safety of the three chloroprocaine dosages (30 mg chloroprocaine isobaric 1 % ; 40 mg chloroprocaine isobaric 1 % ; 50 mg chloroprocaine isobaric 1 %) on the basis of incidence of transient neurological symptoms (TNS)
 - o Incidence of adverse events (AEs)
 - o Vital signs (electrocardiograms (ECGs), blood pressure (BP), heart rate (HR), and oxygen saturations (SpO2))

CHL1/02-2014:

- Safety endpoints:
 - o To investigate the safety and tolerability of the administered chloroprocaine 1% doses on the basis of the incidence of treatment-emergent adverse events, in particular TNS
 - o Vital signs and ECG

CHL1/02-2006/M

- Safety endpoints:
 - o Incidence TNS after 24 hand 7 days
 - o AEs
 - o Incidence of cardiovascular adverse events (hypotension, bradycardia)
 - o Vital signs (ECG abnormalities, BP, HR, and SpO2)

CHL1/01-2012/M

- Safety endpoints:
 - o Incidence of neurological adverse events, in particular, transient neurological symptoms (TNS) and Cauda Equina Syndrome (CES)

7.1.2 Categorization of Adverse Events

The Sponsor used MedDRA version 18.1 to identify preferred terms for adverse events for Phase 2 study CHL1/02-2014, Phase 4 study CHL1/01-2012M, postmarketing AE, and AEs derived from the literature (Phase 2 study CHL1/02-2004 was originally reported as a literature reference). MedDRA version 11.1 was used to identify preferred terms for AEs for earlier Phase 3 study CHL1/02-2006/M.

The CRO that prepared AE data files for the ISS checked the preferred terms between these two MedDRA versions relevant to the AEs from each of these sources and confirmed that the preferred terms are the same.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Sponsor analyzed safety data by pooling three clinical studies (CHL1/02-2014, CHL1/02-2006/M, and CHL1/02-2012/M). Safety data from the original Phase 2 study (CHL1/02-2004) was not included in the pooled data analysis.

In addition, twenty-two studies in the published domain (including the Sponsor's originally conducted Phase 2 study CHL1/02-2004) were pooled together.

Ideally, the original Phase 2 study should have been included in the pooled safety data since all Case Report Forms were available to the Sponsor. However, given the low incidence of adverse events and the small sample size of that study, the overall pooled data presented by the Sponsor is acceptable.

Adverse events (AEs) from the European postmarketing (pharmacovigilance) safety database have been presented separately (not integrated with phase 2/3/4 or literature-based AE data) since the denominator for these postmarketing AEs is unknown. Consequently, only the numbers of postmarketing AEs were presented in AE tables, not percentages.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The tables below summarize the number of subjects treated with intrathecal chloroprocaine in the entire clinical development program, including Phase 4 study, as well as number of subjects per dose.

Table 29 Number of Subjects Dosed with Intrathecal Chloroprocaine

Study	Number of Subjects
CHL1/02-2004	44
CHL1/02-2014	45
CHL1/02-2006/M	66
CHL1/01-2012/M	392
Total	547

(Source: NDA 208791 Sponsor's Integrated Summary of Safety)

Table 30 Number of Subjects Per Dose of Intrathecal Chloroprocaine 1% in Sponsor-conducted Clinical Studies

	Dose of Intrathecal Chloroprocaine HCl 1%						
	30 mg	31 to < 40 mg	40 mg	41 to < 50 mg	50 mg	> 50 mg	Unknown
CHL1/02-2004	14	N/A	15	N/A	15	N/A	N/A
CHL1/02-2014	15	N/A	15	N/A	15	N/A	N/A
CHL1/02-2006/M	N/A	N/A	N/A	N/A	66	N/A	N/A
CHL1/01-2012/M	1	53	106	86	131	14	1
Total	30	53	136	86	227	14	1

N/A = Not Applicable

(Source: NDA 208791 Sponsor's Integrated Summary of Safety and Clinical Study Report for Study CHL1/01-2012/M).

A total of 547 subjects were exposed to intrathecal chloroprocaine in the development program. Slightly less than half (241 subjects (44%)) received a dose of 50 mg or greater. Another 222 (41%) were exposed to doses of 40 to < 50 mg (i.e., 80% of the proposed marketing dose). However, the majority (337/463) of the subjects who received ≥ 40 mg dose were in the open label Phase 4 study. The safety data from the Phase 4 study is not as robust, given that there was no blinding or control arm present. Overall, since there is vast amount of general knowledge available in literature about the class of drug, including the approved Reference Listed Drug, Nesacaine, the exposure at the 50 mg dose or above is adequate.

See Section 6.1.2 for dose and demographic information for Studies CHL1/02-2004, CHL1/02-2014, CHL1/02-2006/M, and CHL1/01-2012/M. Phase 4 Study (CHL1/01-2012/M) has the largest number of subjects, as well as the largest number of subjects > 65 years old (refer to Table 31 below for dosing by age group).

Table 31 Chloroprocaine Dose Data by Age Group for Study CHL1/01-2012/M

Chloroprocaine dose (mg)	All (N = 392)	Age < 65 years (N = 306)	Age > 65 years (N = 87)
Mean	44.49	44.77	43.51
SD	6.22	6.12	6.50
Median	44.00	45.00	40.00
Range	0 – 70	0 – 60	30 – 70

(Source: NDA 208791 Sponsor's Final Study Report for Study CHL1/01-2012/M)

Similar mean and median doses were given in subjects < 65 years old and those > 65 years old. In these calculations, the Sponsor included all subjects enrolled in the study, including one subject (Subject 003-076), who did not receive intrathecal chloroprocaine due to puncture failure, and was therefore documented as receiving a dose of zero milligrams.

7.2.2 Explorations for Dose Response

During the development program, three doses of chloroprocaine were evaluated in adult subjects. Table 30 summarizes the number of subjects exposed to each dose. The majority of subjects who received doses less than 50 mg were in the Phase 4, open-label study. The Phase 4 study was not blinded and lacked a control arm, and the Sponsor did not provide pertinent data regarding surgical start time, surgical duration, or times of IV rescue medication administration for subjects who received less than 50 mg of chloroprocaine. Therefore, meaningful assessment of dose response could not be made and a formal evaluation of dose-dependent adverse events was not performed.

7.2.3 Special Animal and/or In Vitro Testing

The Sponsor's preclinical information was evaluated by Drs. Imran Khan and Jay Chang of the Pharmacology-Toxicology review team. The animal program was generally considered acceptable. For further details, refer to the Pharmacology-Toxicology review document.

7.2.4 Routine Clinical Testing

Clinical laboratory data (blood chemistry, urinalysis, and hematology) were not collected in the phase 2/3/4 clinical studies. Vital sign data were collected in the Phase 2 studies (CHL1/02-2004 and CHL1/02-2014) and Phase 3 study (CHL1/02-2006/M), but not the Phase 4 study (CHL1/01-2012/M). ECG data were collected only during the Phase 3 study (CHL1/02-2006/M).

In the Summary of Clinical Safety, the Sponsor states (verbatim):

As reported by internationally recognized guideline (CPMP/ICH/364/96, § 2.5.1) the effect of anaesthesia [sic] is dramatic, occurs as expected after treatment and is unlikely to have occurred spontaneously, the success of the anaesthesia [sic] can be evaluated with objective assessments. The anaesthetic [sic] qualities are associated primarily to physicochemical properties of the LA. Moreover, the efficacy of the procedure is evaluable by objective parameters by the physician, without any need to apply a laboratory test. Similarly, the safety assessments are based on evident evaluations routinely performed by the physician. Therefore, laboratory values have not been included during the study design.

Moreover during the phase 4 safety study, the common clinical practice is followed and no clinical laboratory evaluations are foreseen.

The non-clinical studies conducted by the Sponsor did not reveal any laboratory abnormalities in the animal models. Given this information, the breadth of knowledge available in literature regarding other ester-type local anesthetics and their mechanism of action, it is appropriate to assume that alterations in clinical laboratories would be highly unlikely.

The routine monitoring of subjects was adequate in terms of vital signs and ECG.

7.2.5 Metabolic, Clearance, and Interaction Workup

Chloroprocaine is rapidly metabolized by systemic pseudocholinesterase to its metabolite 2-chloro-4-aminobenzolic acid (ACBA). Plasma concentrations of chloroprocaine and its metabolite ACBA and urinary ACBA excretion were investigated as secondary end-points in the second Phase 2 study (CHL1/02-2014).

The results of study CHL1/02-2014 demonstrated that chloroprocaine was not quantifiable in plasma after the spinal injection, whereas its metabolite, ACBA, was quantifiable in most plasma samples. Plasma ACBA concentrations increased in plasma after the spinal injection of the parent compound and reached a peak 30 min post-dose. Plasma ACBA concentrations showed proportionality to the increase in chloroprocaine dose. The percent amount of excretion of ACBA was approximately 1.70% with all 3 doses (30 mg, 40 mg, and 50 mg).

Because intrathecal chloroprocaine 50 mg, the maximum proposed intrathecal dose, does not achieve measureable systemic (plasma) exposure, systemic drug-drug interactions are highly unlikely. Therefore, no systemic drug-drug interaction studies on intrathecal chloroprocaine or its major metabolites or in-vitro studies assessing the potential for systemic drug interactions have been performed. Furthermore, no in-vitro or systemic in-vivo drug interaction studies have been identified in the literature on intrathecal chloroprocaine or its metabolites.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The Sponsor presented both historical and current published data available in literature on adverse events for different formulations of chloroprocaine and other local anesthetics utilized in epidural and intrathecal injection. The evaluation performed by the Sponsor was adequate. See Section 2.4 of this review for additional discussion regarding neurological adverse events associated with previous formulations of chloroprocaine, as well as other local anesthetics given intrathecally.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during any of the clinical studies conducted by the Sponsor. No deaths were reported in the postmarketing safety reports.

7.3.2 Nonfatal Serious Adverse Events

No serious adverse events (SAEs) occurred in studies CHL1/02-2004, CHL1/02-2014, and CHL1/01-2012/M.

Three SAEs occurred in the Phase 3 study CHL1/02-2006/M. All three occurred in the bupivacaine group, and one occurred prior to study drug administration.

- Subject 102: 63-year-old male randomized to intrathecal bupivacaine had a small surgical tool broken in the knee joint during knee arthroscopy. Subject recovered completely.
- Subject 126: A 69-year-old male randomized to intrathecal bupivacaine underwent transurethral resection of the prostate. Subject suffered from transurethral resection syndrome characterized by nausea, vomiting, bradycardia and sweating. Subject treated appropriately and recovered on the same day of intervention.
- Subject 204: 58-year-old female randomized to intrathecal bupivacaine underwent knee arthroscopy. After premedication with midazolam, the subject suffered Quincke's edema at the eyelids due to an allergic reaction to the premedication. The event lasted 2 hours and 25 minutes. The patient was treated with 4 mg dimetiden, 50 mg ranitidine and 250 mg methylprednisolone. The subject completely recovered.

7.3.3 Dropouts and/or Discontinuations

During the clinical development program, chloroprocaine was administered as a one-time injection into the intrathecal space. Since there were no doses were repeated and the drug is not given via infusion, discontinuation of administration was not possible in any of the conducted studies.

Nearly all subjects in the chloroprocaine-treatment groups completed the studies. A total of two subjects were discontinued from the Phase 2 studies (one subject from each study). Both subjects were discontinued prior to administration of intrathecal chloroprocaine. Two subjects in the chloroprocaine arm were discontinued in the Phase 3 study (CHL1/02-2006/M). One of the subjects had a sensory block only to L1, but was able to undergo with procedure with only one intraoperative dose of anxiolytic. The other subject was deemed a treatment failure because no sensory block was achieved

and therefore, general anesthetic was administered instead. In comparison to the chloroprocaine arm, the bupivacaine arm had seven subjects discontinued due to failure to achieve desired level of block, with three of the seven cases, requiring general anesthesia.

Six patients discontinued the Phase 4 study (CHL1/01-2012/M); 1 for adverse event (Subject 03-076 discontinued from study due to procedural complication of injection failure due to anatomic reasons), 4 lost to follow-up (Subjects 05-009, 05-017, 05-024, 05-037), 1 reported as “other” (Subject 04-002 with serious alterations of cardiac conduction, who was enrolled but did not receive the study medication, therefore was withdrawn from the study).

The only adverse events that led to subject discontinuation were anesthesia insufficient (CHL1/02-2006/M study only) and anesthetic complication (CHL1/01-2012/M) (Preferred Term). There were no dose-dependent adverse events that led to subject discontinuation.

7.3.4 Significant Adverse Events

No significant non-serious adverse events occurred during the Phase 2, 3, or 4 studies.

7.3.5 Submission Specific Primary Safety Concerns

Chloroprocaine has been on the market since 1955, indicated for local infiltration, epidural injection, and peripheral nerve blocks. Its safety profile has been well characterized for the approved indications. Chloroprocaine is not approved for intrathecal injection. However, there are literature reports on the safety of intrathecal chloroprocaine due to accidental intrathecal injection during epidural placement, as well as, general off-label intrathecal use by physicians in clinical practice.

One major safety concern with intrathecal local anesthetics, in particular, lidocaine, has been the possibility of causing neurologic adverse events like TNS or CES. Due to this concern, the Sponsor conducted a Phase 4 safety study (CHL1/01-2012/M) in order to assess the incidence of neurological complications associated with intrathecal chloroprocaine administration. In addition, the Sponsor conducted a literature search and provided a summary of the current literature data with regards to intrathecal chloroprocaine and the current standard-of-care intrathecal drug, bupivacaine. The results of the Phase 4 study are discussed in Section 7.4.1. The results of the literature search are discussed in Section 7.7.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study CHL1/02-2004

The original data was not available for review for Phase 2 study CHL1/02-2004. However, the Sponsor was able to provide a study report which contained the following table describing adverse events:

Table 32 Adverse Events for Study CHL1/02-2004

Adverse Event	Chloroprocaine 1% - 30 mg N = 14		Chloroprocaine 1% - 40 mg N = 15		Chloroprocaine 1% - 50 mg N = 15	
	During Surgery	Follow- up period	During Surgery	Follow- up period	During Surgery	Follow- up period
Hypotension			1		1	
Bradycardia	3					
Pain	3			1		2
Nausea	1	1		1		
Vagal reaction	1					
Lower limb clonia	1					
Vomiting		1				
Unusual sensation						3
Opening of suture		1				
Total	9	3	1	2	1	5

(Source: Clinical Study Report for Study CHL1/02-2004)

Due to the low number of adverse events, the Sponsor did not perform statistical analyses of the events. All of the adverse events listed in the table above were reported as resolved.

Bradycardia, pain, and unusual sensation were to most common adverse events reported. Definition of "unusual sensation" was not provided in the study report. Hypotension and bradycardia are commonly described side effects of spinal anesthetics. The site of pain is not stated in the study report. Pain at the site of surgery during the surgical procedure would imply a failed or incomplete spinal, which may have multiple etiologies (i.e., poor spinal technique, individual's unique anatomical differences, positioning, or actual drug itself). Pain at the site of spinal injection can also occur, particularly if more than one spinal attempt is necessary. Post-operative pain may have many other etiologies, but is expected to occur once the spinal anesthetic

starts to wear off. Therefore, given the nature of the adverse events reported, there are no new safety concerns regarding intrathecal chloroprocaine.

Hypotension was only seen in the 40 mg and 50 mg dose cohorts, and therefore, may be dose dependent. However, given the low number of subjects and the low number of adverse events, no definitive conclusions can be drawn regarding dose-dependency of adverse events.

Study CHL1/02-2014

The table below lists the adverse events in Phase 2 study CHL1/02-2014.

Table 33 Adverse Events with at Least 2% Occurrence by SOC and PT for study CHL1/02-2014

	Actual Treatment			
	Chloroprocaine 1% - 30 mg N = 15	Chloroprocaine 1% - 40 mg N = 15	Chloroprocaine 1% - 50 mg N = 15	Total N = 45
	Count (%)	Count (%)	Count (%)	Count (%)
Cardiac disorders		1(6.7)		1(2.2)
Bradycardia		1 (6.7)		1 (2.2)
Gastrointestinal disorders		1(6.7)	1(6.7)	2(4.4)
Diarrhea		1 (6.7)		1 (2.2)
Vomiting		1 (6.7)		1 (2.2)
Nausea		1 (6.7)	1 (6.7)	2 (4.4)
General disorders and administration site conditions	2 (13.3)	3 (20)	3 (20)	8 (17.8)
Injection site pain	2 (13.3)	3 (20)	3 (20)	8 (17.8)
Infections and infestations	1 (6.7)			1 (2.2)
Osteomyelitis	1 (6.7)			1 (2.2)

	Actual Treatment			
	Chloroprocaine 1% - 30 mg N = 15	Chloroprocaine 1% - 40 mg N = 15	Chloroprocaine 1% - 50 mg N = 15	Total N = 45
	Count (%)	Count (%)	Count (%)	Count (%)
Injury, poisoning and procedural	14 (93.3)	13 (86.7)	13 (86.7)	40 (88.9)
Procedural pain	14 (93.3)	13 (86.7)	13 (86.7)	40 (88.9)

The most common adverse events reported were procedural pain and injection site pain (see discussion above). These events were recorded post-operatively and the Sponsor postulated that the high incidence of procedural pain was due to the fact that the sensory block induced by intrathecal chloroprocaine wears off quickly. The number of subjects that experienced these adverse events appear to be evenly distributed amongst the three different doses of chloroprocaine. Therefore, no conclusions can be drawn regarding dose-dependency of adverse events.

Study CHL1/02-2006/M

The table below lists the most frequently observed adverse events by system organ class as well as their dictionary-derived terms for Phase 3 study CHL1/02-2006/M.

Table 34 Most Frequent AEs for Study CHL1/02-2006/M

		Bupivacaine 0.5% (10 mg)		Chloroprocaine 1% (50 mg)		Total
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	
Injury, poisoning and procedural complications	Anesthetic complication	3	4.7	1	1.5	4
	Foreign body trauma	1	1.6			1
	Transurethral resection syndrome	1	1.6			1
Vascular disorders	Hypotension	1	1.6	4	6.1	5
General disorders and administration site conditions	Injection site pain	2	3.1			2
	Pain	1	1.6			1
Nervous system disorders	Headache	1	1.6	1	1.5	2

		Bupivacaine 0.5% (10 mg)		Chloroprocaine 1% (50 mg)		
Body System or Organ Class	Dictionary-Derived Term	Count	%	Count	%	Total
Cardiac disorders	Bradycardia	1	1.6			1
Gastrointestinal disorders	Vomiting	1	1.6			1
Metabolism and nutrition disorders	Hyperglycemia			1	1.5	1
Musculoskeletal and connective tissue disorders	Muscle spasms	1	1.6			1
Skin and subcutaneous tissue disorders	Angioedema	1	1.6			1

Overall, more adverse events were reported in the bupivacaine group than in the chloroprocaine group. The most frequent adverse event reported in the chloroprocaine group was hypotension. As mentioned above, hypotension is a known adverse event associated with spinal anesthesia and its frequency of occurrence in this study is not concerning. One adverse event of hyperglycemia occurred in subject 207 in the chloroprocaine group. Subject 207 had known type II diabetes. Given the nature of the adverse events reported and the low frequency, there are no new safety concerns regarding intrathecal chloroprocaine.

Study CHL1/01-2012/M

This study was a prospective, observational, multicenter study, to evaluate the relationship between intrathecal chloroprocaine 1% and the onset of all possible neurological adverse events, with particular attention to TNS and CES, in adult patients undergoing short surgical procedures (< 40 minutes). Two follow-up questionnaires specifically designed were distributed at 24 hours and 7 days after spinal injection of chloroprocaine, to gather a wide range of possible neurological complications.

The table below summarizes the adverse events in Study CHL1/01-2012/M.

Table 35 All Adverse Events for Study CHL1/01-2012/M

Primary system organ class Preferred term	All (393)	
	N	%
Subjects with at least one adverse event	37	9.41
Cardiac disorders	4	1.02
Bradycardia	4	1.02
Gastrointestinal disorders	2	0.51
Vomiting	2	0.51
General disorders and administration site conditions	6	1.53
Drug effect incomplete	4	1.02
Drug ineffective	1	0.25
Injection site pain	1	0.25
Injury, poisoning and procedural complications	12	3.05
Anesthetic complication	3	0.76
Incision site haemorrhage	1	0.25
Incision site pain	1	0.25
Post lumbar puncture syndrome	6	1.53
Procedural hypotension	1	0.25
Musculoskeletal and connective tissue disorders	1	0.25
Myalgia	1	0.25
Nervous system disorders	9	2.29
Burning sensation	1	0.25
Headache	1	0.25
Hypoaesthesia	2	0.51
Hypotonia	2	0.51
Paresthesia	4	1.02
Respiratory, thoracic and mediastinal disorders	1	0.25
Hyperventilation	1	0.25
Vascular disorders	13	3.31
Hypotension	13	3.31

(Source: Sponsor's CHL1/01-2012/M Final Study Report)

Overall, 37 patients (9.4%) experienced at least one AE (a total of 48 AEs). One patient with an AE was withdrawn from the study (patient 03-076, due to procedural complications of injection failure due to anatomic reasons). The most common events were hypotension (3.35%), post-lumbar puncture syndrome (headache and frequent vomiting) (1.53%), and bradycardia (1.02%).

There were fourteen subjects who selected symptoms (fatigue, nausea/vomiting, dizziness, urinary/defecation problems) on the follow up questionnaire. Only five of the fourteen subjects had reported an AE (7 AEs total): 3 hypotension, 1 vomiting, 1 pain at surgical site, and 2 post puncture headache. All were mild or moderate in severity, with no SAE. Five AEs recovered, one changed in intensity (headache), and one was lost at follow up (pain at surgical site).

To characterize the events reported by patients during questionnaire interviews, the Investigators were requested to perform a complete diagnostic evaluation (i.e., CT, MRI,

electromyography, etc.) in the cases of suspect neurological adverse events, to obtain the diagnosis and prescribe adequate treatment. No patients required a CT, MRI, or electromyography studies. Two subjects required “other” diagnostic investigations:

- Subject 04-035 presented signs of an affection of the saphenous nerve (possible surgical complication) – follow up was recommended in the community.
- Subject 04-052 was seen by the Department of Plastic surgery where “little area distal to skin incision” was reported. According to the physician, findings were mild and related to surgery.

Although there were no reports of Transient Neurological Symptoms (TNS) or Cauda Equina Syndrome (CES), there were two subjects who reported symptoms on their post-operative questionnaire that were suspicious for TNS. Pertinent subject summaries and conclusions are as follows:

- Subject 03-001
 - o 55-year-old male, 95 kg (BMI 33.2), undergoing knee gonalgia surgery
 - o No other pertinent medical/surgical history
 - o Received 50 mg of intrathecal chloroprocaine 1% and did not experience paresthesia either during puncture or during surgical procedure
 - o Received as post-operative analgesia metamizole and oxycodone on the day of surgery
 - o At Visit 2, 24 hours post-surgery, the subject reported to have experienced moderate pain at site of injection/surgery and unusual sensations of moderate level at anterior thighs (burning and tingling). Subject reported good general sensation. Subject admitted to have had these symptoms in the past.
 - o At Visit 3, 7 days post-surgery, subject reported that pain at site of surgery and site of injection improved and the unusual sensations were no longer present
 - o Conclusion: given that the subject experienced the “unusual sensations” of anterior thigh burning and tingling prior to spinal administration, and TNS is typically defined as pain and/or abnormal sensation in the buttocks and lower extremities, it does not appear that this subject’s symptoms were consistent with the diagnosis of TNS
- Subject 05-043
 - o 24-year-old female, 55 kg (BMI 19.5), undergoing screw removal knee surgery
 - o Medical history: depression on daily escitalopram
 - o Received 35 mg of Chloroprocaine 1% and did not experience paresthesia either during puncture or during surgical procedure
 - o Received as post-operative analgesia paracetamol and ketoprofen on the day of surgery

- At Visit 2, 24 hours post-surgery, the subject reported to have experienced mild-moderate pain at the site of injection/surgery and mild unusual sensations at buttocks, anterior thighs and one side (tingling, numbness and hypoesthesia). Subject reported good general sensation.
- At Visit 3, 7 days post-surgery, subject reported pain at site of surgery and site of injection improved, and the unusual sensations were no longer present
- Conclusion: Limited details regarding the subject's symptomatology make it difficult to make any definitive conclusions regarding her final diagnosis. However, given that the patient noted unusual sensations in the buttock and thighs which began within 24 hours of intrathecal injection, and resolved in several days, TNS cannot be ruled out.

When considering the entire development program (both Phase 2 studies, Phase 3 study, and Phase 4 study), a total of 547 subjects were dosed with intrathecal chloroprocaine. Subject 05-043 in Phase 4 study was the only subject with possible diagnosis of TNS, which would be an incidence of 0.18%. This is lower than the incidence that is quoted by Goldblum et. al., in 2013, which was 0.6% (Goldblum, 2013). Therefore, there are no additional safety concerns regarding TNS with intrathecal chloroprocaine at this time.

The Sponsor did not provide raw data sets for the Phase 4 study, and the original Final Study Report did not contain information regarding the breakdown of doses administered to subjects experiencing adverse events. The Sponsor was asked to provide this information and submitted the following pertinent data in a response to Information Request on August 2, 2017.

Table 36 Selected Dose-Dependent Adverse Events by Preferred Term for Study CHL1/01-2012/M

System Organ Class Preferred Term	CP >30 to 40 mg N=159 n (%)	CP >40 to <50 mg N=86 n (%)	CP 50 mg N=131 n (%)	CP >50 mg N=14 n (%)
Subjects with at least one AE	4 (2.5%)	4 (4.7%)	26 (19.9%)	2 (14.3%)
Cardiac disorders Bradycardia	2 (1.3%)	0 (0.0%)	2 (1.53%)	0 (0.0%)
Vascular disorders Hypotension	2 (1.3%)	0 (0.0%)	9 (6.9%)	2 (14.3%)
Nervous system disorders	0 (0.0%)	2 (2.3%)	7 (5.3%)	0 (0.0%)

(Source: NDA 208791 Sponsor's response to Information Request dated August 2, 2017)

The table above depicts adverse events of interest for intrathecal chloroprocaine. Cardiac adverse events like bradycardia and hypotension are known to occur with all intrathecal local anesthetics, and are typically dose-dependent. The data from this Phase 4 study appears to be consistent with what is clinically expected. Although the > 50 mg dose had a lower incidence of bradycardia and hypotension in this study, there were low number of subjects in that dose cohort, and the range of doses above 50 mg is unclear. Therefore, it is reasonable to conclude that adverse events of hypotension and bradycardia are dose-dependent.

Nervous system disorders (PTs: burning sensation, headache, hypoesthesia, hypotonia, and paresthesia) also appeared to have a dose-dependent trend. However, it is often difficult to determine the etiology of such events because patient-derived factors and spinal technique-derived factors may be the cause of such events instead of the actual local anesthetic. Therefore, final conclusions regarding dose-dependent neurologic adverse events cannot be made at this time.

7.4.2 Laboratory Findings

Clinical laboratory data (blood chemistry, urinalysis, and hematology) were not collected in the phase 2/3/4 clinical studies.

7.4.3 Vital Signs

Vital signs data were collected from the studies CHL1/02-2004, CHL1/02-2014, and CHL1/02-2006/M, but not from Phase 4 study, CHL1/02-2012/M. The Sponsor did not perform an integrated data analysis of vital signs from these studies.

Study CHL1/02-2004

Original data from the study is not available for review. Therefore, all information regarding vital signs was acquired from the official study report.

Clinically relevant hypotension was defined as a decrease in systolic arterial blood pressure by 30% or more from baseline. Clinically relevant bradycardia was defined as heart rate decrease below 45 beats per minute (BPM). The heart rate cut-off of 45 BPM was derived by the Sponsor and not cleared with the FDA prior to study initiation abroad. The inclusion criteria included subjects ASA class I – III and the exclusion criteria did not exclude subjects with cardiac disorders. Therefore, although a heart rate low of 45 BPM may have been adequate in a healthy adult trial, given that this study enrolled ASA III subjects who may have had underlying cardiac conditions, such a low heart rate cut-off may not be appropriate. Also, there is a discrepancy in the study report where a table in Section 12.2.1 states that three subjects experienced bradycardia, however, study report Section 12.5.1 states, “Clinically relevant

bradycardia requiring administration of atropine during the procedure was reported in 5 patients of group 30 only ($p = 0.001$) [post-hoc analysis showed a p value of 0.013 as compared to group 40 and a p value of 0.013 as compared to group 50].” This incidence appears higher than what is typically seen in clinical practice, and is particularly surprising given that such high degree of bradycardia appeared in the lowest dose cohort. However, given the small sample size and the fact that bradycardia is a known adverse event associated with spinal anesthetic administration, no new safety conclusions can be drawn regarding the results of this study.

Two subjects experienced clinically relevant hypotension (one in the 40 mg and one in the 50 mg group).

The Sponsor reports that although systolic and diastolic arterial blood pressure and heart rates were lower in all three chloroprocaine groups after spinal administration, they were not able to detect differences amongst the three groups in their post-hoc analysis.

CHL1/02-2014

Definitions of clinically relevant hypotension and clinically relevant bradycardia from study CHL1/02-2004 were also used for this study.

Only two subjects had reported vital signs adverse events during the study. Subject 007 experienced transient bradycardia twenty-two minutes after spinal injection of chloroprocaine 40 mg, which required intravenous atropine treatment. Subject 004 (chloroprocaine 40 mg group), who had baseline arterial hypertension (150/84), experienced hypertension during the course of the study, but no higher than baseline.

CHL1/02-2006/M

Definitions of clinically relevant bradycardia and hypotension were not provided in the study protocol or study report.

Sinus bradycardia (<60 bpm) occurred at a frequency ranging from 64 (bupivacaine group) to 69 (chloroprocaine group) percent in the two groups, however only one subject in the bupivacaine group had bradycardia coded as an adverse event.

Four (6.1%) subjects in chloroprocaine group (Subjects 117, 311, 319, and 347) and one subject (1.6%) in bupivacaine group (Subject 324), suffered from adverse event of hypotension in the intra-operative period. Three out of four events in the test group and the one in the reference group were considered as possible/probably related adverse events to study treatment. Subject 324 also suffered from bradycardia adverse event possibly related to study treatment.

Conclusion

The overall frequency of vital sign-related adverse events for all studies evaluated was low. All of the adverse events discussed (except for one episode of hypertension in a subject with baseline hypertension) were bradycardia and hypotension, which are well known and clinically expected after intrathecal local anesthetics. Therefore, these data do not present a new safety signal.

7.4.4 Electrocardiograms (ECGs)

ECG data were collected at screening during the Phase 3 study CHL1/02-2006/M only. ECG (12-lead) parameters at baseline are tabulated per group (56 subjects in test treatment group and 55 subjects in reference treatment group). No statistical difference among the treatment groups was found. In the group treated with 50 mg plain chloroprocaine 1%, 13 subjects had at least one ECG abnormality at the screening and in the group treated with 10 mg Bupivacaine 0.5%, 22 subjects had at least one abnormality. None of the ECG abnormalities detected at screening were found to be clinically relevant.

In the Phase 3 study, ECGs were also obtained during surgery “before intrathecal block and thereafter until end of anesthesia (if possible and foreseen by standard hospital procedures). Therefore, such ECGs were not obtained in all patients.” (Source: NDA 208791 Sponsor’s Integrated Summary of Safety). Twenty-one subjects in the chloroprocaine group and twenty-two subjects in the bupivacaine group had intraoperative ECG. The Sponsor did not specify how many ECG leads were used for intraoperative ECGs. Two subjects experienced intraoperative sinus tachycardia (HR > 100 bpm) in the chloroprocaine group. Six subjects experienced abnormal ECG findings intraoperatively in the bupivacaine group (four subjects with sinus bradycardia (HR < 60 bpm) and 1 subjects with sinus tachycardia). The number and the type of ECG abnormalities reported are not clinically significant. No other arrhythmias were reported for either the chloroprocaine or the bupivacaine groups.

7.4.5 Special Safety Studies/Clinical Trials

No additional special safety studies were conducted by the Sponsor.

7.4.6 Immunogenicity

The Sponsor did not provide information on the immunogenicity of chloroprocaine and it does not appear that there is readily available evidence that chloroprocaine is immunogenic.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Refer to discussion in Section 7.4.1 of this review.

7.5.2 Time Dependency for Adverse Events

Time to adverse event data was only available for studies CHL1/02-2014 and CHL1/02-2006/M. Most adverse events occurred within 24 hours of the study drug administration, although some occurred within minutes (e.g., hypotension). Findings were similar between chloroprocaine and bupivacaine in the Phase 3 study.

7.5.3 Drug-Demographic Interactions

The Sponsor performed an evaluation of adverse event incidence rates for chloroprocaine by the sub-populations of age, race, and gender for the pooled datasets from the second Phase 2 (CHL1/02-2014), Phase 3 (CHL1/02-2006/M), and Phase 4 (CHL1/01-2012/M) studies. However, not all data from the Phase 4 study were included since this study was not completed at the time the analysis was performed. The intrinsic factor groups were defined as:

- Age (18-40 vs. 41-65 vs. >65 years of age)
- Gender (male vs. female)
- Race (Caucasian vs. African American vs. Asian vs. Hispanic vs. Other)

The Sponsor's findings are reported below.

Age

For chloroprocaine in the Phase 2/3/4 trials, each of the 18-40 year old, 41-65 year old and >65 year old age groups have a similarly low frequency for all, and any given, AE. There appear to be no discernable differences in the nature and frequency of AEs for chloroprocaine across the three age groups. Of note, the least number of patients were enrolled in the > 65 years old subgroup (107/547 subjects dosed):

- Study CHL1/02-2004: 13 subjects
- Study CHL1/02-2014: 0 subjects
- Study CHL1/02-2006/M: 7 subjects
- Study CHL1/01-2012/M: 87 subjects

Per the Sponsor's analysis, there was a slightly higher incidence of related TEAEs in subjects > 65 years old who received 40 mg to < 50 mg and 50 mg of intrathecal chloroprocaine than those who received < 40 mg. The Sponsor's states (verbatim):

Evaluation of each preferred term related TEAE by dose in the “40 to <50” and “50 mg” dose categories shows that the numeric frequency of any given related TEAE never exceeded n=2 in any given age group for any given dose category. The frequencies are so low that comparisons are not meaningful. (Source: NDA 208791 Sponsor’s Integrated Summary of Safety)

The age- and dose-related analysis performed by the Sponsor is difficult to interpret for the following reasons:

- Analysis was not performed for all TEAEs, but rather only TEAEs deemed “related” to the intrathecal chloroprocaine. Since limited information is available on how “relatedness” was assessed, there is a possibility that certain TEAEs were not accounted for in the Sponsor’s analysis.
- Analysis was performed without all the data from the Phase 4 study being available, which had the bulk of the > 65yo population. At the time of the Sponsor’s analysis number of subjects > 65 years old was sixty-six. However, at the conclusion of the Phase 4 study, there were 87 subjects enrolled > 65 years old.
 - In the Phase 4 study final study report, the percent of subjects who had AEs in > 65 years old category (8.05%) was lower than the percent of subjects in the < 65 years old category (9.8%).
 - The Sponsor did not provide an analysis of specific AEs by age in the final study report.
 - The Sponsor did not provide case report forms to identify subjects with any specific adverse events (e.g., hypotension)
 - No dose-related AE analysis was performed by Sponsor for the Phase 4 study.
- Since only a small number of subjects were > 65 years old in the original Phase 2 (13 subjects) and the Phase 3 (7 subjects), and no subjects > 65 years old were enrolled in the second Phase 2 study, the Sponsor did not perform an analysis of adverse events based on age for those individual studies.

Given the overall small number of adverse events in all subjects in all studies, and the limitations of the available data and data analysis, it is difficult to make any definitive safety conclusions about the incidence of age- and dose-related adverse events in the elderly patient population. In general, because the elderly have a higher propensity for multi-systemic disease, in particular cardiovascular disease, it may be reasonable to assume that the elderly may experience a higher rate of cardiovascular adverse events (e.g., hypotension) than their younger counterparts. Language reflecting this assumption is already present in the Nesacaine, as well as intrathecal bupivacaine and intrathecal lidocaine labels. In conclusion, although there is limited data from Sponsor-conducted clinical studies that indicate that the elderly may be at a higher risk of adverse events when given higher doses of chloroprocaine, given the general clinical

experience with other intrathecal local anesthetics in this age group, is it reasonable to include similar language regarding the elderly present in the Nesacaine label also in the intrathecal chloroprocaine 1% label.

Gender

Incidence of AEs in male and females were similar across all studies. Overall, there were no clinically relevant differences in AEs reported between genders.

Race

Treatment-emergent adverse events (TEAEs) were analyzed by available race data. No safety concerns were identified for intrathecal chloroprocaine (all doses) across the races evaluated. However, due to limited sample sizes for non-White races (see Section 6.1.7), definitive conclusions regarding safety across all races cannot be reached.

7.5.4 Drug-Disease Interactions

The Sponsor did not study the effect of intrathecal chloroprocaine on individuals with renal impairment, hepatic impairment, cardiac conditions, or pulmonary conditions. In addition, no studies were conducted in individuals with rare genetic disorders like pseudocholinesterase deficiency or hereditary erythromelalgia, although they would more likely impact drug efficacy than safety. (See Section 6.1.7 for more details)

7.5.5 Drug-Drug Interactions

No systemic drug-drug interaction studies on intrathecal chloroprocaine or its major metabolites have been performed in this drug development program. (See Section 7.2.5 for more details).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity studies were not required of this product due to the acute indication and the short half-life.

7.6.2 Human Reproduction and Pregnancy Data

There is no human reproduction or pregnancy data available for chloroprocaine 1%. Because intrathecal chloroprocaine is rapidly hydrolyzed in plasma and is not measureable in the plasma of adults (confirmed by study CHL1/02-2014), intrathecal

chloroprocaine 1% is not expected to cause reproductive toxicity in females or males of reproductive potential.

7.6.3 Pediatrics and Assessment of Effects on Growth

No assessments of the effects of intrathecal chloroprocaine on growth were made as a pediatric indication is not sought at present.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

An overdose of intrathecal chloroprocaine would be considered a dose greater than that required to produce an adequate spinal anesthetic level for a particular surgical procedure. Alternatively, a dose greater than the to-be-labeled maximum dose (50 mg) could be considered an overdose. Doses as high as 70 mg were administered without serious adverse events in the Phase 4 study. The only adverse event that may be dose related was hypotension, particularly in the > 65 year old subjects (Refer to Section 7.5.3 for in-depth discussion). Overall, the risk from overdose is small, and the most serious adverse events of hypotension and bradycardia, can be monitored and readily treated, if necessary.

Intrathecal chloroprocaine is administered in a controlled setting by medical professionals trained in intrathecal drug administration. It is impossible to self-administer intrathecal chloroprocaine. In addition, it is not structurally similar to known drugs of abuse and undergoes rapid systemic clearance. In the clinical trials, there was no evidence of behavioral changes or alterations in mood or mentation following intrathecal chloroprocaine. Due to all of these factors, chloroprocaine has a negligible abuse potential.

7.7 Additional Submissions / Safety Issues

Sponsor provided an additional assessment of chloroprocaine based on published literature ((cutoff date December 31, 2015). Sponsor was able to identify twenty-two literature publications in support of safety of IT chloroprocaine. Four of these publications ((Breebart et al., 2014; Sell et al., 2008; Casati et al., 2006; Casati et al., 2007) utilized the Sponsor's chloroprocaine 1% product. AEs from the 22 publications were extracted and were included in the Integrated Summary of Safety. The table below provides a summary of the 22 publications.

Table 37 Literature Publications that Support Use of Intrathecal Chloroprocaine

Publication	Treatments	Population	Demographics
Maes et. al., 2015 [Belgium]	CP: 40 mg	Patients planned for elective Cesarean	58 females (18-40y)

	CP: 40 mg + sufentanil 1 µg B: 7.5 mg + sufentanil 1 µg	section	
**Breebart et. al, 2014 [Belgium]	L: 60 mg L: 60 mg + preload CP: 40 mg CP: 40 mg + preload	Day case knee arthroscopy patients	65 males / 35 females L without preload: (mean ± SD= 46 ± 14y) L + preload: (mean ± SD= 44 ± 12y) CP without preload: (mean ± SD= 51 ± 12y) CP + preload: (mean ± SD= 43 ± 12y)
Forster et. al., 2013 [Finland]	A: 40 mg (20 mg/ml) CP: 40 mg (20 mg/ml)	Day case knee arthroscopy patients	A: 10 males/6 females: (mean ± SD= 52 ± 13.6y) CP: 10 males/8 females: (mean ± SD= 48 ± 14.9y)
Pollock, 2012	This review paper on chloroprocaine did not provide details of study treatments.	NS	NS
Vaghadia, et. al, 2012 [Canada]	L: 35 mg (20 mg/ml solution) mixed with 12.5 mg fentanyl (50 mcg/ml) CP: 40 mg preservative-free	Outpatient transurethral prostatectomy patient	40 subjects, genders unknown L : 20 (59–77y) CP: 20: (64–78y)

	(20 mg/ml), mixed with 12.5 mg fentanyl.		
Lacasse, et. al., 2011 [Canada]	B: 7.5 mg CP: 40 mg 2% preservative-free	Elective ambulatory surgery patients	B: 20 males/30 females: (mean $\pm$ SD= 54 $\pm$ 16y) CP: 24 males/29 females: (mean $\pm$ SD= 53 $\pm$ 16y)
Hejtmanek et. al., 2011 [USA]	CP: 20-60 mg (20 mg/ml) L: 30-100 mg B: 4-12 mg P: NS M: NS	Ambulatory surgery patients	CP: 290 males/213 females: (mean $\pm$ SD= 56 $\pm$ 15y) L: 54 males/30 females: (mean $\pm$ SD= 56 $\pm$ 16y) B: 4 males/3 females: (mean $\pm$ SD= 60 $\pm$ 15y) P: 4 males/ 1 female: (mean $\pm$ SD= 62 $\pm$ 15y) M: 2 males: (mean $\pm$ SD= 74 $\pm$ 10y)
Forster et. al., 2011 [Finland]	CP: 40 mg (20 mg/ml) A: 60 mg (40 mg/ml)	Day case knee arthroscopy patients	CP: 31 males/8 females: (mean $\pm$ SD= 45 $\pm$ 12.9y) A: 24 males/15females: (mean $\pm$ SD= 48 $\pm$ 12.4y)
Fu et. al., 2008 [China]	2.5% CP 1.0 mL (Group A) 2.5% CP 1.2 mL	Hysterectomy patients	Group A: 30 females: (mean $\pm$ SD= 41 $\pm$ 10y)

	(Group B) 2.5% CP 1.4 mL (Group C) 2.5% CP 1.6 mL (Group D)		Group B: 30 females: (mean $\pm$ SD=42$\pm$9y) Group C: 30 females : (mean $\pm$ SD=42$\pm$7y) Group D: 30 females: (mean $\pm$ SD=42$\pm$8y) [race unstated]
**Sell et. al., 2008 [Finland]	CP: 35 mg CP: 40 mg CP: 45 mg CP: 50 mg	Elective lower limb ambulatory surgery patients	CP 35: 7 males/9 females: (mean $\pm$ SD= 39$\pm$17y) CP 40: 9 males/7 females: (mean $\pm$ SD= 42$\pm$19y) CP 45: 6 males/10 females: (mean $\pm$ SD= 53$\pm$16y) CP 50: 6 males/10 females: (mean $\pm$ SD= 41$\pm$12y)
**Casati et. al., 2007 [Italy]	L: 50 mg (1% plain) CP: 50 mg (1% preservative-free plain)	Outpatient knee arthroscopy patients	L: 9 males/6 females: (20-69y) CP: 10 males/5 females: (18-70y)
Fu et. al., 2006 [China]	2.2 mL mixture (2.5% chloroprocaine 1.2 mL, 10% glucose 0.5 mL, 3% ephedrine 0.5 mL)	Primiparas with pregnancy periods of over 37 weeks scheduled to undergo Cesarean section	40 females: (mean $\pm$ SD= 27.70 $\pm$ 3.72y)
**Casati et. al., 2006	CP: 30 mg	Lower limb outpatient surgery	CP30: 6 males/ 9 females:

[Italy]	CP: 40 mg CP (1% preservative-free): 50 mg		(mean $\pm$ SD= 59 $\pm$ 13y) CP40: 7 males/ 8 females: (mean $\pm$ SD= 56 $\pm$ 14y) CP50: 8 males/ 7 females: (mean $\pm$ SD= 48 $\pm$ 16y)
Kopacz et.al., 2005 [USA]	CP: 10 mg (2% preservative-free) CP: 20 mg	Healthy volunteers	4 males/ 4 females: (mean $\pm$ SD= 40 $\pm$ 11y)
Gonter et. al., 2005 [USA]	CP: 30 mg (1.5% preservative-free) P: 80 mg	Healthy volunteers	4 males/ 4 females: (mean $\pm$ SD= 42 $\pm$ 11y)
Davis et. al., 2005 [USA]	CP: 30 mg (2% preservative free) with clonidine (15 μ g) CP: 30 mg without clonidine	Healthy volunteers	4 males /4 females: (mean $\pm$ SD= 34 $\pm$ 11y)
Yoos et. al., 2005 [USA]	CP: 40 mg (2 ml 2% CP with 0.25ml of preservative free normal saline) B: 7.5 mg	Healthy volunteers	4 males/ 4 females: (mean $\pm$ SD= 38 $\pm$ 7y)
Yoos et. al., 2004 [USA]	CP: 20 mg CP: 30 mg CP: 40 mg CP: 50 mg CP: 60 mg (all CP of 2.0% conc.)	Spinal anesthesia patients at Mason Medical Center	52 males/ 70 females: (mean $\pm$ SD= 55 $\pm$ 16y)
Warren et. al., 2004	CP: 40 mg	Healthy volunteers	5 males/ 3 females:

[USA]	(preservative- free, 2 mL, 2.0% with 0.25 mL saline) CP: 40 mg (preservative-free, 2 mL, 2.0% with 0.25 mL 10% dextrose)		(mean $\pm$ SD= 37 $\pm$ 10y); in crossover fashion
Smith et. al., 2004 [USA]	CP: 30mg CP: 45 mg CP: 60 mg with and without epinephrine	Healthy volunteers	11 males/ 7 females: (mean $\pm$ SD= 35 $\pm$ 9y)
Vath et. al., 2004 [USA]	CP: 40 mg (2% with saline) CP: 40 mg with 20 μ g fentanyl	Healthy volunteers	3 males/ 5 females: (mean $\pm$ SD= 37 $\pm$ 13y)
Kouri et. al., 2004 [USA]	L: 40 mg 2% CP: 40 mg, 2%, preservative-free	Healthy volunteers	5 males/ 3 females: (mean $\pm$ SD= 35 $\pm$ 6y)

CP = Chloroprocaine; B = Bupivacaine; L = Lidocaine; A = Articaine; M = Mepivacaine;
P = Prilocaine; NS = Not Stated

** Study utilized Sintetica's CP 1% product

(Source: NDA 208791 Sponsor's Integrated Summary of Safety)

Among the 22 published clinical studies, 19 were prospective clinical trials, where the most common doses ranged from 30 to < 50 mg (see Table 38 below). Three studies were retrospective reviews and did not cite the dose of chloroprocaine administered (Pollock, 2012; Hejtmanek, 2011; Yoos, 2004).

Table 38 Number of Subjects in Published Literature by Dose of Intrathecal Chloroprocaine

Post Marketing Data Source	Number of Subjects (%) ^{a,b}					
	Intrathecal Chloroprocaine HCl Solution, Dose, mg					
	N=5199 ^b					
	Unknown	<30 mg	30 to <40	40 to <50	50 mg	>50 mg
Prospective Clinical Trials	64 (1.2%)	38 (0.7%)	136 (2.6%)	300 (5.8%)	30 (0.6%)	6 (0.1%)
Retrospective Clinical Series Reviews ^b	4625 (89.0%)	0	0	0	0	0
Overall Total	4689 (90.2%)	38 (0.7%)	136 (2.6%)	300 (5.8%)	30 (0.6%)	6 (0.1%)

a- Subjects are summarized according to the dose level of the product they actually received.

b- In the 19 prospective trials, in some papers some subjects received chloroprocaine twice; the n=5199 counts these subjects once, not twice. These papers are: [Kopacz, 2005] where 8 subjects were treated twice with Chloroprocaine (10 mg and 20 mg) separated by at least 72 hours, [Vath and Kopacz, 2004] where 8 subjects were treated twice with Chloroprocaine (with Saline solution and with fentanyl), [Smith et al., 2004] where 6 + 6 + 6 subjects were treated twice with Chloroprocaine (alone and with different doses of epinephrine), [Warren and Kopacz, 2004] where 8 subjects were treated twice with Chloroprocaine (with Saline solution and with Dextrose) and [Davis and Kopacz, 2005] where 8 subjects were treated twice with Chloroprocaine (with Saline solution and with Clonidine).

(Source: NDA 208791 Sponsor's Integrated Summary of Safety)

The Sponsor notes that some patients in several studies described above received more than one dose of chloroprocaine, but were counted only once. However, the Sponsor did not account for the fact that the three retrospective studies (4625 subjects) utilized patient data from many of the prospective studies (574 subjects). Therefore, the total number of subjects (5199) is likely erroneous due to some repeated subjects in prospective and retrospective studies. In addition, some of the studies included an intrathecal active comparator (e.g., bupivacaine, lidocaine, etc.). According to the Sponsor, a total of 334 subjects from the 22 literature references discussed above received an active comparator. However, as with the test group, the Sponsor did not account for possible repeat subjects in the retrospective studies.

Upon evaluation of the 19 prospective studies, a total of 575 subjects were dosed with chloroprocaine, which is one more than accounted for by the Sponsor. Eight of these subjects were also dosed with a comparator drug at a different time interval. A total of 210 subjects received a comparator drug (8 of which received chloroprocaine as well).

No deaths were reported in the 22 published studies/articles. Since the authors of these 22 published clinical trials did not assign seriousness to AEs presented in these publications, and similarly, the Sponsor did not assign seriousness to AEs from these publications, no SAE data from these literature based clinical studies are available.

Overall, 185 subjects who received intrathecal chloroprocaine experienced a TEAE. A total of 87 subjects who received a comparator drug experienced a TEAE. These numbers were derived from the Sponsor's evaluation of the literature references in the ISS. Because the Sponsor's total number of subjects is likely to include duplicate subjects, it is impossible to calculate the true incidence of TEAEs. The most frequently-occurring AEs were hypotension, pain, nausea, vomiting, headache, respiratory depression, and bradycardia. Other than pain, the other AEs are all commonly-associated AEs with spinal anesthetics, in general, and thus do not raise new safety concerns. Location of pain is not specified. Since pain at the site of surgery versus pain at the site of spinal injection versus pain in any other site can be attributed to multitude of etiologies, further safety conclusions regarding this AE cannot be made.

In addition, the Sponsor presented the number of related TEAEs by dose. However, given that relatedness could not be properly assessed without more detailed information about each clinical study, and the various confounders (e.g. concomitant intrathecal medications) within the studies, these data were not evaluated for the purposes of this review.

Of note, one case of CES was reported in literature (Vaghadia et. al., 2012).

- The authors presented results of a prospective, randomized, double-blind study which compared lidocaine and chloroprocaine in combination with fentanyl for patients undergoing outpatient transurethral resection of the prostate (TURP). Selective spinal anesthesia was performed in 40 patients either with 40 mg of chloroprocaine mixed with 12.5 µg of fentanyl or 35 mg of lidocaine mixed with 12.5 µg of fentanyl. One patient treated with chloroprocaine developed an incomplete cauda equina like-syndrome within 24 hours, which persisted for several weeks. Patient was 66- years-old and had no pre-existing symptoms of numbness or weakness of the lower extremities or buttocks, and did not suffer from diabetes. He received a spinal injection at L3-4 with a 25G needle. No problem was reported during spinal insertion and there was no concern of drug error or contamination with skin disinfectant. After surgery, he complained of mild left leg weakness, but was able to walk. During the first day at home he experienced numbness in both buttocks extending down the posterior thighs to both feet and weakness. Subsequently, he complained of severe, burning, stabbing pain in his anterior legs bilaterally requiring treatment with oral oxycodone. He also developed urinary retention. His leg weakness improved slowly over 5-6 weeks, but he had persistent numbness in the left buttock and the soles of both feet. Neurological assessment showed sensory loss to pain and temperature in the posterior calf and soles of both feet. The final neurological diagnosis was of a resolving acute cauda equina like-syndrome that may have been caused by spinal anesthesia. The authors conclusions for the overall study were (1) selective spinal anesthesia with chloroprocaine and lidocaine for TURP

have comparable results for clinical characteristics, and (2) further research on TNS and cauda equina risk with chloroprocaine is warranted.

One additional case of CES was reported in the postmarketing database. The case is discussed in Section 8 below.

There is conflicting literature on the possible etiologies of CES, with both local anesthetics and spinal injection technique being implicated. In 1991, reports of CES after continuous spinal anesthesia using micro-catheters were published. The cause of CES was thought to be due to pooling of large amounts of local anesthetic at the lumbosacral roots, leading to excessive exposure and toxic effects. Some laboratory studies implicated the preservative sodium bisulfite and the presence of low pH as possible causes for neurological deficits. (Taniguchi, 2004)

In the Clinical Anesthesia textbook published in 2009, Dr. Barish discusses the possible mechanisms by which local anesthetics produce CES. In vitro evidence suggests that local anesthetics can produce excitotoxic damage by depolarizing neurons and increasing intracellular calcium concentrations. Other studies demonstrate that local anesthetics can cause neuronal injury by damaging neuronal plasma membranes through detergent like actions or by activation of phospholipase-C. It is also unclear whether adjuncts added to local anesthetics (e.g. epinephrine) contribute to CES. Based on animal studies, it has been argued that epinephrine should not be added to intrathecal lidocaine (Barash, 2009).

Since bupivacaine is approved for intrathecal use and is also considered the drug-of-choice for intrathecal administration (over approved intrathecal lidocaine), the Sponsor was asked to provide an in-depth literature assessment of the incidence of transient neurologic syndrome and cauda equina syndrome with chloroprocaine in comparison to bupivacaine.

The Sponsor reviewed published literature and identified five studies which compared chloroprocaine to bupivacaine. Four studies were prospective clinical trials (Yoos et. al. 2005, Lacasse et. al., 2011, Maes et. al. 2015, and Teunkens et. al., 2016) and one was a retrospective review (Hejtmanek et. al., 2011). The total number of subjects was 744 (631 treated with chloroprocaine and 121 treated with bupivacaine). Only two cases were described as possible symptoms of TNS (Lacasse et. al., 2011). A summary of the above studies is adapted from the Sponsor's response to the Information Request dated May 11, 2017.

Table 39 Incidence of TNS in Literature Studies Comparing Bupivacaine and Chloroprocaine

Author and Year	Local Anesthetic	Dose (mg)	Number of Subjects	Number of TNS
Yoos et. al., 2005	2-Chloroprocaine 20 mg/ml*	40 mg	8**	0
	Bupivacaine 5 mg/ml*	7.5 mg	8**	0
Hejtmanek et. al., 2011	2-Chloroprocaine 20 mg/ml*	20-60 mg	503	0
	Bupivacaine (strength unknown)	4-12 mg	7	0
Lacasse et. al., 2011	2-Chloroprocaine 20 mg/ml*	40 mg	53	1
	Bupivacaine 7.5 mg/ml	7.5 mg	53	1
Maes et. al., 2015	2-Chloroprocaine 10 mg/ml*	40 mg	19	0
	2-Chloroprocaine 20 mg/ml + Sufentanil*	40 mg + 1 mcg	18	0
	Hyperbaric Bupivacaine 7.5 mg/ml + Sufentanil**	9 mg + 1 mcg	19	0
Teunkens et. al., 2016	2-Chloroprocaine 10 mg/ml*	40 mg	30	0
	Bupivacaine 5 mg/ml	7.5 mg	34	0

* Chloroprocaine preservative-free

** Volunteer subjects treated in twice; they received the two spinal anesthetics separated by at least 96 hours

(Source: NDA 208791 Sponsor's response to Information Request dated May 11, 2017).

In their retrospective study, Hejtmanek et. al., reviewed spinal anesthetics for 601 subjects. The majority of patients (503) received intrathecal chloroprocaine 20 mg/ml. Other local anesthetics that were used included lidocaine (84), bupivacaine (7), prilocaine (5), and mepivacaine (2). Surgical procedure breakdown with percentage of cases in lithotomy or flexed-knee position in parentheses include the following: 231 (80%) genitourinary, 185 (66%) orthopedic, 133 general surgery, and 52 (65%)

gynecologic procedures. Twenty-nine patients received more than one chloroprocaine spinal anesthetic on separate occasions during the study period. A 73-year-old, ASA II male had six spinals with chloroprocaine for repeat cystoscopies. The authors discovered that urinary retention was the most common side effect in the recovery room, however, 83% of patients had procedures that increase the risk of urinary retention despite the type of anesthetic, and the incidence was equivalent among chloroprocaine and lidocaine spinal anesthetics. No subjects experienced neurological AEs such as CES or TNS. In their summary, the authors of this review estimate that since 2004, approximately 44,000 spinal anesthetics with chloroprocaine were administered at their institution. During that time period, there were four reports of patients that had symptoms consistent with TNS. The authors concluded that the incidence of TNS with intrathecal chloroprocaine appears to be extremely low, especially when compared to lidocaine, however, additional prospective studies are needed.

Among the other four prospective studies, only two possible cases of TNS were identified by Lacasse et. al., one in the chloroprocaine group and one in the bupivacaine group. There were fifty-three subjects per group, therefore, the incidence of TNS in this study is 1.9% for each drug. Per the authors of the study, both patients that experienced TNS shared important characteristics (verbatim):

Both patients were 50 to 60-yr-old females undergoing transobturator tension-free urethral suspension (TVT-O) in the lithotomy position. Differential diagnosis includes the well-described neuropathies known to be associated with the lithotomy position. According to a review by Warner et al., there was a 1.5% incidence of lower extremity neuropathies in patients who underwent general anesthesia and surgery while in the lithotomy position. Positioning the thighs in extreme abduction with external rotation, as is occasionally the case during TVT-O, is a well described risk factor. Another potential etiology could be surgical trauma, often entrapment of the obturator nerve during placement of the sling. In a review of the complications associated with transobturator sling procedure, Boyles et al. found four cases of neuropathy out of a total of 173 complications described in an 18-month period. Therefore, we can't confirm the diagnosis of TNS in either of these patients. (Lacasse, 2011)

Four additional TNS cases were reported to the Sponsor in their postmarketing database. These cases are discussed in Section 8 below. No cases of cauda equina syndrome or TNS were reported in the Phase 2, 3, or 4 studies.

With regard to CES, the Sponsor identified nine literature references that discussed ten subjects with possible CES after a bupivacaine spinal anesthetic. The cases had many confounders, including concomitant intrathecal administration of other agents. Therefore, in several of the cases, definitive diagnosis of CES could not be made. Overall, the data presented from literature confirms that the incidence of TNS and CES

for both chloroprocaine and bupivacaine is quite low. Other factors, like type of surgical procedure, use of catheters, puncture technique, patient positioning, etc., cannot be dismissed as possible contributing etiologies to CES and TNS. However, the incidence of permanent neurological deficits, even in subjects that develop CES and TNS is exceedingly low, and therefore, no additional safety concerns or safety monitoring is warranted at this time.

8 Postmarket Experience

First European market approval for Sintetica's intrathecal chloroprocaine was granted on March 19, 2012. The postmarketing (pharmacovigilance) safety database, which is part of the ISS database, includes AEs from European postmarketing reports to the following companies:

- Sintetica which markets Ampres in Germany and Austria. Their Ampres® product is registered but not marketed in Spain.
- Amdipharm Mercury Company Limited (AMCo) which markets Ampres® in the UK. Their Ampres® product is registered but not marketed in Ireland.
- Nordic Pharma which markets Ampres® in Belgium and CLOROTEKAL® in France.
- L Molteni & C. dei F.lli Alitti which markets Ampres® in Poland. Their Decelex® product is registered but not marketed in Italy.

Each of the above formulations is the same as the product which is the subject of this NDA. The Sponsor is the holder of the global safety database for these products and receives all individual case safety reports (ICSRs) from local distributors under a Safety Data Exchange Agreement (SDEA). AEs from these ICSR were included in the postmarketing (pharmacovigilance) safety database in the Integrated Summary of Safety of the NDA.

The table below summarizes the number and the source of the case reports.

Table 40 Postmarketing Pharmacovigilance Database Reports

Source	Number of Subjects
ICSRs as Spontaneous Reports	127
ICSRs from Other Postmarketing Study Reports from Solicited Sources (Nordic Pharma's CLOCK and BAG studies)*	337 (CLOCK: 328; BAG: 9)

Total	464
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* CLOCK (Pharmacoepidemiology Study on Real Life Impact of Chloroprocaine (CLOROTEKAL®) on the Eligibility for Discharge From Hospital of Patients Requiring Short Outpatient Surgery Under Spinal Anesthesia) and BAG (Factors Influencing the Choice of Anesthesia (Spinal Anesthesia or Short General Anesthesia) in Outpatient Surgery) clinical studies were performed by Nordic Pharma, the sponsor of CLOROTEKAL® (chloroprocaine HCl 1% (10 mg/mL) solution for injection) which is approved in Europe for intrathecal injection. Sintetica obtained these safety data from Nordic Pharma by contractual agreement. At the time of the NDA submission, according to ClinicalTrials.gov, CLOCK study has been completed and the BAG study was in the process of recruitment. At the time of this NDA review, both studies were completed; however, no results have been published.
(Source: NDA 208791 Sponsor's Integrated Summary of Safety)

The table below lists treatment emergent SAEs from postmarketing pharmacovigilance safety reports by system organ class.

Table 41 Treatment-Emergent SAEs from European Postmarketing Database

System Organ Class ² Preferred Term ²	Chloroprocaine ¹ n
Subjects with any Serious Treatment-emergent Adverse Event	54
Injury, poisoning and procedural complications	47
Anesthetic complication	47
Delayed recovery from anaesthesia	1
Urinary retention postoperative	1
Nervous system disorders	7
Headache	2
Cauda equina syndrome	1
Dysesthesia	1
Hypoesthesia	1
Hypoesthesia oral	1
Loss of consciousness	1
Motor dysfunction	1
Paresthesia	1
Cardiac disorders	3
Cardiac arrest	3
Respiratory, thoracic and mediastinal disorders	2
Respiratory depression	2
Renal and urinary disorders	1
Urinary retention	1
Vascular disorders	1
Hypotension	1

Cut-off Date: 31DEC2015

Note 1: Subjects are summarized according to the product they actually received

Note 2: MedDRA dictionary

(Source: NDA 208791 Sponsor's Integrated Summary of Safety)

Fifty-four SAEs were reported, the vast majority (47) were anesthetic complications which included (1) anesthesia insufficient (40 cases), (2) high and prolonged spinal block (1 case), and (3) unintentional total spinal block (3 cases), and (4) transient radicular irritation due to spinal anesthesia (3 cases).

Per the Sponsor's assessment, a total of 464 subjects with TEAEs have been reported for over 200,000 units marketed as of the ISS data cutoff date of December 31, 2015. The most common TEAEs were incision site pain (n=156), anesthetic complication (n=131), injection site pain (n=72), hypotension (n=67), back pain (n=63), paresthesia (n=58), nausea (n=46), headache (n=44), dizziness (n=27), bradycardia (n=22), anxiety (n=20), and vomiting (n=15). These TEAEs are consistent with those seen in the Phase 2, 3, and 4 studies and for spinal local anesthetics in general.

The most serious of the postmarketing safety reports are one case of cauda equina syndrome and three cases of cardiac arrest. These cases are described and discussed below.

Three cases of cardiac arrest reported are described as follows:

- Case S/BE/CHL/2014-003; 201400161 (spontaneous report)
 - o Healthy 45-year-old male (175 cm and 78 kg), with no relevant medical history and no known drug allergies (NKDA) was scheduled to undergo a knee arthroscopy, and therefore received 30 mg of chloroprocaine 1% (intrathecal) at L3/L4.
 - o The patient was placed in the supine position without inclination of the operating table during surgery and he was preloaded with 500 ml Hartmann's solution (sodium lactate compound solution). No other concomitant medication was reported. A total spinal block developed requiring resuscitation: after 7-8 minutes, extreme bradycardia was observed resulting in cardiac arrest. A precordial thump was given and 0.5 mg atropine was injected, leading to recovery of normal sinus rhythm. A short period of loss of consciousness was reported (no further details regarding chronology). No additional vasoactive drugs were administered. There were no further cardiac problems during the procedure. Normal recovery of the block after 60 minutes. No further abnormality of cardiac rhythm over six subsequent hours was detected. The patient recovered without sequelae and was discharged from the hospital on the same day in the evening.
 - o It is unlikely that this case represents a "total spinal" because a total spinal would not be easily reversed by a single dose of atropine, which occurred in this case. A hypervagal state with vasomotor paralysis is a more likely etiology.
- Case S/BE/CHL/2014-343; 201402163 (spontaneous report)

- o A female patient of unspecified age, 23-weeks pregnant, who received 35 mg of chloroprocaine 1% intrathecal for an unspecified procedure. The patient developed a sudden drop in blood pressure leading to cardiac arrest. Cardiac arrest was immediately treated by cardiac massage and injection of atropine. After a follow up, anesthesiologist reported the event as “vasovagal reaction”. Nevertheless the company decided to maintain the wording “cardiac arrest” because cardiac massage was performed and atropine was administered. No other information is available by the physician but, following the case, a healthy baby girl (3kg, good Apgar score) was delivered by Caesarean section uneventfully.
 - o Although the anesthesiologist called this event a “vasovagal reaction,” limited details regarding the timing of arrest with regard to timing of spinal, type of surgery, fluid status, blood loss, concomitant medications administered, etc., are not available. Therefore, conclusions about true etiology of the “arrest” cannot be made.
- Case S/BE/CHL/2015-069; 201501711 (spontaneous report)
 - o Healthy 40-year-old male (165 cm, 75 kg) with no relevant past medical history was undergoing knee arthroscopy and received intrathecal chloroprocaine 1% (dose unspecified) at L2/L3. Around twelve minutes following the induction of anesthesia, the patient developed sudden bradycardia (heart rate < 45 beats per minute). He received 0.5 mg of atropine, but went on to develop asystole. The patient was administered 0.1 mg of epinephrine and cardiac massage was performed for 3 to 5 minutes. The patient subsequently regained sinus rhythm and the surgery was completed. The patient received propofol and sufentanil by intravenous route for sedation. The patient recovered without sequelae.
 - o Limited information regarding the case is available. Baseline vital signs are unknown. It is unclear whether intravenous fluids were administered prior to or during spinal administration. The cardiac arrest may have been caused by the spinal anesthetic, but without additional information about the case, final conclusions cannot be made.

Cardiac arrest after spinal anesthesia is a rare event. The incidence varies between 1.3 and 18 per 10,000 (Sostaric, 2013). Sprung et al., conducted a retrospective review of 518,294 anesthetics during a 10 year period and reported the frequency of cardiac arrest for patients undergoing regional anesthesia to be 1.5 per 10,000, which is less than the reported frequency of cardiac arrest for patients receiving general anesthesia (5.5 per 10,000) (Sprung, 2003).

Unlike cardiac arrest, hypotension and bradycardia are the most common side effects seen with sympathetic denervation produced by a spinal anesthetic. Bradycardia after

spinal occurs at a higher incidence in healthy young individuals, who typically have lower baseline heart rates (Lesser, 2003). Pollard, et. al., similarly reported that a baseline pulse of <60 bpm was associated with a fivefold increase in the odds of developing moderate bradycardia during spinal anesthesia. Typically, young patients have strong vagal tone, and ASA physical status I patients have a threefold increased risk for developing moderate bradycardia during spinal anesthesia. Current therapy with β -blockers or block height above T6 were also important risk factors for bradycardia identified in the Pollard study (Pollard, 2001).

Bupivacaine hydrochloride 0.75% (NDA 016964) is the most commonly used local anesthetic in the United States for subarachnoid block. The current package insert for bupivacaine states, "The most commonly encountered acute adverse experiences which demand immediate countermeasures following the administration of spinal anesthesia are hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia. These may lead to cardiac arrest if untreated. In addition, dose-related convulsions and cardiovascular collapse may result from diminished tolerance, rapid absorption from the injection site, or from unintentional intravascular injection of a local anesthetic solution."

The postmarketing database presented by the Sponsor consists of cases collected from 2012 until December 31, 2015. With regard to the three cardiac arrest cases, the Sponsor states that the denominator of these cases is unknown. However, over 200,000 units of single-dose chloroprocaine 1% were marketed in Europe. Using this data, the incidence of cardiac arrest with chloroprocaine is approximately 0.15 cases per 10,000, which is less than reported by literature for spinal anesthesia (Sprung, 2003). Even if there is significant underreporting of the cardiac arrest cases, the incidence of cardiac arrest with chloroprocaine does not appear to be greater than with other intrathecal local anesthetics.

Given the rare, but well described, phenomenon of cardiac arrest with spinal anesthesia and the proposed labeling language, the three cardiac arrest cases discussed above from the postmarketing database do not warrant any further scrutiny.

In addition to the case discussed in Section 7.7, there was one additional case of CES reported in the postmarketing database. This case is discussed below.

- Case FR150115AMP007 (Local Reference Number 201500030)
 - o A 55-year-old male received 50 mg of intrathecal chloroprocaine 1% for a knee arthroscopy. Patient reported to have preexisting spinal canal pathology (details not provided). The spinal was administered at a high level per report (but level not identified). During the intervention, hypotension was reported, however, no details were provided. The spinal anesthetic lasted for two hours, however, patient experienced dysesthesia for fifteen days following surgery. In addition, patient experienced urinary

retention. The patient reported a “few days” of urinary disorder (unspecified), numbness in legs and one hand, associated with incapacity to kneel down. The initial differential diagnosis included CES, TNS, spinal hematoma, and spinal ischemia. An MRI was obtained, which did not reveal a lesion that could explain the symptomatology. Upon 2nd follow-up, the French Authority (Agence Nationale de Sécurité du Médicament et des Produits de Santé), which assessed the case, concluded that it was “probable Cauda Equina Syndrome” and “Neuropathy.”

- o Pertinent details of this case, like what preexisting spinal pathology the patient was diagnosed with, the full details of his symptoms, including length of time the symptoms were experienced and pertinent neurological physical exam findings are not available. It is difficult to attribute causality or to confirm the diagnosis of CES without further details.

In addition to one CES case, there were four reports of TNS cases received by the Sponsor.

- Case BE-NORDICGR-201400212 (January 29, 2014)
 - o Surgical procedure: Transobturator Tape (TOT procedure)
 - o Outcome: complete recovery (March 31, 2014)
 - o Symptoms developed as the sensory block wore off and manifested as burning pain in the area previously anesthetized (bilateral sciatica, lumbar, and perineal pain). Motor block was prolonged (150 min). Patient also experienced urinary retention. Neurologic exam and MRI and CT of the lumbar spine were unremarkable. Somato-sensory evoked potentials were normal in the lower limbs.
- Case BE-NORDICGR-201401501 (August 26, 2014)
 - o Surgical procedure: Arthroscopy
 - o Outcome: complete recovery (10-12 hours following surgery)
 - o Patient returned to the hospital 4-5 hours after surgery for stabbing pain in the posterior upper portion of the right thigh, which radiated to the calf and foot. Patient received Dipidolor (piritramide) with complete resolution of the pain. The anesthesiologist stated that the pain may have been caused by intrathecal Ampres or the presence of a plaster bandage.
- Case FR-NORDICGR-201401543 (September 25, 2014)
 - o Surgical procedure: TOT procedure
 - o Outcome: complete recovery 15 days after surgery
 - o Patient returned to the emergency room two days following surgical procedure due to hypoesthesia and paresthesia (burning sensation in both anterior thighs). No motor deficits were present. The patient was given a diagnosis of radicular irritation. Lyrica (pregabalin) 25 mg was prescribed.
- Case FR-NORDICGR-201500254 (February 17, 2015)
 - o Surgical procedure: Arthroscopy
 - o Outcome: recovered, although date not available

- o One day after surgery the patient reported pain and heaviness sensation in sacrum, spreading to the mid-thighs, associated with paresthesia. Upon follow-up approximately a week later, the patient reported significant regression of his symptoms. Further attempts at follow-up were unsuccessful.

Two of the subjects above had TOT procedures which require lithotomy positioning. This position and the procedure itself have been linked to increased incidence of post-operative neuropathies (Lacasse, 2011). Limited data is available for all four cases, so definitive conclusions about the TNS diagnosis cannot be made.

The overall data presented in the postmarketing database does not raise new safety concerns for intrathecal chloroprocaine.

9 Appendices

9.1 References

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9.2 Labeling Recommendations

The Sponsor is relying upon both some clinical and most non-clinical information present in the Nesacaine label. This is reasonable in some sections of the label. However, due to the fact that Nesacaine is approved for different routes of administration (infiltration, nerve block, and epidural), certain language pertinent to the routes of administration for Nesacaine is not pertinent to intrathecal chloroprocaine.

The following changes are recommended:

- Section 1 (INDICATIONS AND USAGE) (b) (4)
 - CLOROTEKAL® (chloroprocaine hydrochloride) is indicated for intrathecal injection for the production of subarachnoid block (spinal anesthesia) in adults undergoing surgical procedures (b) (4)
- Section 2.1 (Recommended Dosing) should only include the 50 mg dose (b) (4)
 - To obtain an effective block to the T 10 level with one single administration in an adult of average height and weight (approximately 70 kg), the recommended dose is 50 mg (b) (4)
- Sponsor needs to update Table 1 (TEAEs in Controlled Trials (Phase 2 and Phase 3)) to only include the 50 mg dose. Also, TEAEs from the original Phase 2 study (CHL1/02-2004) need to be included.
- Sponsor needs to revise Table 2 (Post-Marketing Reports of Adverse Drug Reactions) to only include AE Preferred Terms.
- The proposed language for Section 14 (CLINICAL STUDIES) is not appropriate given that the Sponsor presented analysis of endpoints which were not utilized for evaluation of drug efficacy. Instead, new language should be included regarding the efficacy evaluation of the following endpoint:
 - The proportion of patients who were able to complete the surgical procedure without the need for supplementary intravenous analgesic or sedation drugs

- Average surgical procedure durations, as well as times from intrathecal chloroprocaine injection to surgery start, should be reported in SECTION 14.
- In addition, the Sponsor needs to provide evidenced-based justification or clarification for the following statements:
 - Contraindications:
 - Intravenous regional anesthesia (the anesthetic agent is introduced into the limb and allowed to set in while tourniquets retain the agent within the desired area)
 - Severe anemia

(b) (4)

9.3 Advisory Committee Meeting

No advisory committee meeting was conducted for this application.

9.4 NDA Cycle Events

Table 42 Timeline of Pertinent NDA Review Cycle Events

Meeting/Communication/Date (Supporting Document)	Event/Key Clinical Issues
NDA Submission August 26, 2016 (SD 1)	NDA received.
NDA Filing October 25, 2016	NDA filed.
Information Request (IR) December 15, 2016	Sponsor asked to provide rationale for repeating the Phase 2 study (original study performed in 2004) in 2015 after the completion of the Phase 3 study.
Sponsor response to IR and several clinical items in the 74-day letter December 23, 2016 (SD 7)	Sponsor provided rationale for chosen inferiority margin. Sponsor provided narrative summary for Subject 205 in Phase 3 study (CHL1/02-2006/M) who was withdrawn due to an

	adverse event. Sponsor stated that the Phase 2 study was repeated in order to obtain pharmacokinetic (PK) data requested by the FDA, which was not done in the first Phase 2 study. There were no other differences in the two studies in terms of study design, endpoints, and procedures. However, more subjects required rescue anesthesia/analgesia in the original Phase 2 study (CHL1/02-2004) than in the second Phase 2 study (CHL1/02-2014).
Information Request January 3, 2017	Requested Sponsor to provide all available data, Case Report Forms, and study report for the original Phase 2 study (CHL1/02-2004).
Sponsor response to IR and several clinical items in the 74-day letter January 26, 2017 (SD 10)	Sponsor provided rationale to support small safety sample size. Sponsor provided rationale to support primary efficacy endpoints chosen for studies CHL1/02-2014 and CHL1/02-2006/M. Sponsor submitted a legacy pdf file containing study report, protocol, protocol amendments and deviations, Case Report Form, and adverse event listings for study CHL1/02-2004. Original datasets could not be recovered.
Information Request January 30, 2017	Requested all operating room records for studies CHL1/02-2014, CHL1/02-2006/M, and CHL1/02-2004, and requested analyses of records, in particular surgical procedure length, (b) (4) Sponsor asked to provide additional supporting efficacy data or rationale why it

	is not necessary, for the 30 mg and 40 mg doses of chloroprocaine. Requested that the Sponsor revise the ISE to include more details regarding study CHL1/02-2004. Requested rationale for differences seen in efficacy of two nearly identical Phase 2 studies. Requested the time of all concomitant medication administration in study HL1/02-2006/M. Requested a comprehensive summary on 123 European post-marketing cases of “anesthesia insufficient.”
Sponsor response to Information Request February 17, 2017 (SD 13)	The Sponsor agreed to gather all Case Report Forms and operating rooms records for all three studies and submit them as soon as possible. The Sponsor provided graphical and tabulated data on surgical procedure lengths, time of chloroprocaine administration, time of “readiness for surgery,” surgical start and end times (when available), surgical procedure length (when available), all rescue medications given in the operating room, and time of those rescue medications (when available) for all three studies. (b) (4) Sponsor provided justification for differences in efficacy seen in the two nearly identical Phase 2 studies.

	Sponsor submitted a revised ISE. Sponsor provided a summary of all subjects that were deemed to have insufficient surgical block in study CHL1/02-2006/M. Time of rescue medications was provided, when available. Sponsor provided analysis of European post-marketing data on cases labeled as “anesthesia insufficient.”
Sponsor response to Information Request March 17, 2017 (SD 15)	Sponsor submitted all Case Report Forms available for all three studies, as well as most of operating room records for all three studies. Sponsor indicated that the remainder of the operating room records will be submitted when available. (All operating room records submitted were illegible). Case Report Forms for study CHL1/02-2004 were in Italian.
Information Request March 28, 2017	Requested additional information for fourteen subjects that required rescue medications in study CHL1/02-2004. Requested translated of Case Report Forms for study CHL1/02-2004.
Sponsor response to Information Request March 30, 2017 (SD 16)	Sponsor submitted 28 operating room records for study CHL1/02-2006/M.
Sponsor response to Information Request April 7, 2017 (SD 17)	Sponsor submitted additional information for fourteen subjects that required rescue medications in study CHL1/02-2004. Times of rescue medications were estimated based on examination of operating room records. Sponsor submitted translated Case Report Forms for study CHL1/02-2004.
Information Request April 11, 2017	Requested an update on Phase 4 study (CHL1/01-2012/M), times of intraoperative rescue medications for Phase 3 study (CHL1/02-2006/M), and rationale for

	differences in incidence of rescue medications at Marburg study site for study CHL1/02-2006/M.
Sponsor response to Information Request April 14, 2017 (SD 19)	Sponsor stated that Phase 4 study is complete and final study report will be available mid-May. Sponsor provided several additional times of rescue medications for study CHL1/02-2006/M, however, was not able to provide times of all relevant rescue medications. Sponsor stated that possible difference in amount of rescue medications required at Marburg site for study CHL1/02-2006/M may be attributed to characteristics of subjects treated and to site-specific practice.
Review Extension Memorandum April 20, 2017	Sponsor notified that due major amendment submitted on March 17, 2017 (see above), the review clock has been extended. The new PDUFA date is September 26, 2017.
Information Request April 21, 2017	Sponsor asked to provide completed study report for study CHL1/01-2012/M and update appropriate sections of the NDA with any new safety data. Sponsor also asked to conduct an in-depth literature assessment for the incidence of transient neurologic syndrome (TNS) and cauda equina syndrome (CES) with intrathecal chloroprocaine in comparison to intrathecal bupivacaine.
Sponsor response to Information Request May 11, 2017	Sponsor provided preliminary results of Phase 4 Study CHL1/01-2012/M and indicated that the final report will be submitted shortly. Sponsor also provided their literature assessment of the incidence of TNS and CES with intrathecal chloroprocaine and bupivacaine.
Sponsor response to Information Request May 30, 2019	Sponsor submitted Complete Study Report (CSR) for study CHL1/01-2012/M
Information Request June 1, 2017	Sponsor asked to provide assessment of unexpectedly high failure rate noted in study report CHL1/01-2012/M. Sponsor also asked to provide detailed distribution of chloroprocaine doses for all subjects in

	study CHL1/01-2012/M, and in particular, for the subjects who were considered failures.
Sponsor response to Information Request June 9, 2017	Sponsor provided list of all subjects who were received intraoperative rescue medications, including the medications that were given, as well as their assessment of the failure rate. Sponsor also provided dose of IT chloroprocaine administered and times between IT chloroprocaine and surgical start time for those patients.
Information Request June 13, 2017	Sponsor asked to provide surgical durations for all subjects in Phase 4 study that required intraoperative rescue medications.
Information Request June 14, 2017	Sponsor asked to provide time of rescue medication administration for all subjects in Phase 4 study that required intraoperative rescue medications.
Sponsor response to Information Request June 28, 2017	Sponsor submitted (via e-mail) a table with times of surgery start, intraoperative rescue medication, and duration of surgery for some of the subjects in Phase 4 study that required intraoperative rescue medications. Sponsor indicated that additional data will be forthcoming.
Sponsor response to Information Request July 21, 2017 (SD 24)	Sponsor submitted additional data regarding surgical start, surgical duration, and time of intraoperative rescue medication for subjects in Phase 4 study that required intraoperative rescue medications.
Information Request July 24, 2017	Sponsor asked to provide narrative summaries and Case Report Forms (CRFs) for two subjects in Study CHL1/01-2012/M who had neurological adverse events suspicious for Transient Neurologic Symptoms. Sponsor also asked to provide a table with adverse events based on dose of chloroprocaine for the same study.
Sponsor response to Information Request August 2, 2017 (SD 25)	Sponsor provided narrative summaries and CRFs for subjects in study CHL1/01-2012/M who had neurological adverse

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	events suspicious for Transient Neurologic Symptoms. Sponsor also provided a table with adverse events based on dose of chloroprocaine for the same study.
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9.5 Clinical Investigator Financial Disclosure

Covered Clinical Study (Name and/or Number): CHL1/02-2004, CHL1/02-2014, CHL1/02-2006/M

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: <u>11</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

No concerns about the Investigator's financial interests are present.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALLA T BAZINI
08/10/2017

LEAH H CRISAFI
08/10/2017