23 July 2020
EMA/CHMP/450646/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ZYNRELEF

International non-proprietary name: bupivacaine / meloxicam

Procedure No. EMEA/H/C/005205/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AP135 Triethylene glycol poly(orthoester) excipient
AP Applicant's Part (or Open Part) of a ASMF
AS Active substance
API Active Pharmaceutical Ingredient
AR Assessment Report
ASM Active Substance Manufacturer
ASMF Active Substance Master File = Drug Master File
BCS Biopharmaceutics Classification System
CEP Certificate of Suitability of the EP
CHMP Committee for Medicinal Products for Human use
CMA Critical Material Attributes
CVMP Committee for Medicinal Products for Veterinary use
CFU Colony Forming Units
CMS Concerned Member State
CoA Certificate of Analysis
CPP Critical process parameter
CQA Critical Quality Attribute
CRS Chemical Reference Substance (official standard)
DMSO Dimethyl sulfoxide
DoE Design of experiments
DP Decentralised (Application) Procedure
DPM Drug Product Manufacturer
DPMT N,N-dimethyl-p-toluidine
DSC Differential Scanning Calorimetry
EDQM European Directorate for the Quality of Medicines
EC European Commission
EP European Pharmacopoeia
EU European Union
FDA Food and Drug Administration
FMEA Failure mode effects analysis
FPM Finished Product Manufacturer
FT-IR Fourier Transform Infrared Spectroscopy
GC Gas Chromatography
GC-MS Gas chromatography mass spectrometry
GMP Good Manufacturing Practice
GPC Gel permeation chromatography
GVS Gravimetric vapour sorption
HDPE High Density Polyethylene
HPLC High performance liquid chromatography
HRMS High resolution mass spectrometry
IC Ion chromatography
ICP-OES Inductively coupled plasma-optical emission spectroscopy
ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC In-process control
ICP-MS Inductively coupled plasma mass spectrometry
IR Infrared
IU International Units
IUPAC International Union of Pure and Applied Chemistry
IVR In vitro release
KF Karl Fischer titration
LC Label claim
LCMS Liquid chromatography mass spectrometry
LDPE Low density polyethylene
LLA Luer lock applicator
LOD Loss on drying
LDPE Low Density Polyethylene
LMW Low molecular weight
LOA Letter of Access
LoD Limit of Detection
LOQ Limit of Quantitation

LoQ	List of Questions
LT	Less than
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MMA	Methylmethacrylate
MMD	Molecular mass distribution
Mn	Number average molecular weight
MS	Mass Spectrometry
Mw	Weight average molecular weight
ND	Not detected
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOR	Normal Operating Range
OMCL	Official Medicines Control Laboratories
OOS	Out of Specifications
PAR	Proven Acceptable Range
PBS	Phosphate buffered saline
PDE	Permitted Daily Exposure
PDI	Polydispersity index
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PP	Polypropylene
QbD	Quality by design
QC	Quality Control
QOS	Quality Overall Summary
QP	Qualified person
QTPP	Quality target product profile
QWP	Quality Working Party
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of an ASMF
RRT	Relative retention time
RSD	Relative standard deviation
SmPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
THF	Tétrahydrofurane
TLC	Thin layer chromatography
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Heron Therapeutics B.V. submitted on 8 March 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Zynrelef, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 November 2018. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant scientific innovation.

The applicant applied for the following indication: Zynrelef is indicated in adults for application into the surgical site to reduce postoperative pain for 72 hours.

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for fixed combination products.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0013/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (EMEA-002246-PIP01) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
20 July 2017	EMEA/H/SA/3574/1/2017/SME/III	Walter Janssens, Marion Haberkamp

The Scientific advice pertained to the following aspects:

- Adequacy of the non-clinical package to support the safety of HTX-011 for the proposed Phase 3 local administration studies in visceral and somatic models.
- Adequacy of the available hepatic impairment clinical data for bupivacaine and meloxicam; the available renal impairment data for bupivacaine and meloxicam are sufficient; that renal impairment studies with HTX-011 are not required and that drug-drug interaction (DDI) studies with HTX-011 are not required for the planned MAA.
- Design and adequacy inclusion/exclusion criteria and primary endpoint, statistical plan for the clinical efficacy study Phase 3 studies in visceral (herniorrhaphy) and somatic (bunionectomy) models to support MAA.
- Design and adequacy of safety data base to support the MAA.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: Natalja Karpova

The appointed co-rapporteur had no such prominent role in Scientific advice relevant for the indication subject to the present application.

The application was received by the EMA on	8 March 2019
The procedure started on	28 March 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	1 July 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	18 June 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	5 July 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 July 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 December 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	03 February 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 February 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	27 February 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	29 March 2020
The Rapporteurs circulated the Joint Assessment Report on the	20 April 2020

responses to the List of Outstanding Issues to all CHMP members on	
The CHMP agreed on a second list of outstanding issues in writing and in Oral explanation to be sent to the applicant on	30 April 2020
The applicant submitted the responses to the second CHMP List of Outstanding Issues on	22 June 2020
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	20 July 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Zynrelef on	23 July 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Pain is defined by the International Association for the Study of Pain (IASP) as ''an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Pain can be described as acute or chronic according to its duration. Acute pain is considered adaptive, in that it has a warning function. It is of short duration (generally up to a few weeks) and declines with the healing of the underlying injury or disease. Pain after surgery is a predictable part of the postoperative experience (Apfelbaum 2003). However, like all pain, postoperative pain is complex and multidimensional. Up to 70% of patients have moderate to severe pain after surgery, and the most severe pain occurs within the first 72 hours.

2.1.2. Epidemiology

Pain is one of the most widespread conditions affecting patient health and quality-of-life. Postoperative pain, one of the most serious forms of acute pain, remains an area of particularly high unmet medical need. A study of 56 World Health Organization member states estimated that annually 234.2 million major surgical operations take place worldwide. This translates into about one surgery each year for every 25 people (Chapman 2013). Surgery induces important disturbances in body homeostasis such as hypercatabolism, hypercoagulability, and inflammation, leading to a series of symptoms and signs such as hypoxaemia, pain, nausea, vomiting, ileus, sleep disturbances, and fatigue, and complications including pneumonia and myocardial infarction (Bonnet 2005). Postoperative pain is often the predominant symptom (Bonnet 2005).

Postoperative pain remains an important problem despite notable advances in the scientific understanding of pain in recent decades. It has been suggested that less than half of patients who undergo surgery report adequate postoperative pain relief (Apfebaum 2003). Following surgery, 65% of patients experience moderate-to-severe pain. Following discharge, 46% of patients still suffer from moderate-to-severe pain, and pain remains the leading cause of unanticipated hospital readmission following surgery. A review of data on postoperative pain on the first day following surgery in 105 German

hospitals, 2 found that high pain scores can result from almost all surgical procedures, including those that appear minimally traumatic (Chapman 2013). However, it also has been reported that orthopaedic surgeries are among the major generators of intense postoperative pain (Chapman 2013).

Importantly, poor management of postoperative acute pain may lead to the development of chronic pain. This occurs in 10%–50% of patients after various common operations (Khelet 2006; Meissner 2015). Once pain has become chronic, it is generally regarded as maladaptive and difficult to treat as patients' response to currently available treatments is highly variable. Multiple and complex mechanisms are frequently involved, including somatic, psychological and socioeconomic factors. Associated disorders such as depression, anxiety and sleep disturbances may have an additional impact (Guideline on the clinical development of medicinal products intended for the treatment of pain; EMA/CHMP/970057/2011). Prevention of chronic postsurgical pain involves risk factors detection and evaluation, appropriate anesthetic support and effective postoperative pain management. Intensity of acute postoperative pain correlates with the risk of developing a persistent pain state (Khelet 2006).

2.1.3. Aetiology and pathogenesis

According to IASP website, acute pain after surgery has a distinct pathophysiology that reflects peripheral and central sensitization as well as humoral factors contributing to pain at rest and during movement. Surgical tissue trauma leads to nociceptor activation and sensitization. As a result, individuals suffer ongoing pain at rest and increased responses to stimuli at the site of injury. Different surgical procedures involve distinct organs and specific tissue within and adjacent to them, creating a variety of patterns of nociceptor sensitization and differences in the quality, location, and intensity of postoperative pain. Mediators released locally and systemically during and after surgery that contribute to nociceptor sensitization include: prostaglandins, interleukins, cytokins and neurotrophins. Decreased tissue pH and oxygen tension, and increased lactate concentration, persist at the surgical site for several days. These responses may contribute to peripheral sensitization and spontaneous pain behaviour following an incision. Nerves may be injured during surgery and hence discharge spontaneously. Spontaneous action potentials in damaged nerves may account for qualitative features of neuropathic pain that may be present early in the postoperative period and can evolve into chronic neuropathic pain. Noxious input during and after surgery can enhance the responses of nociceptive neurons in the CNS (central sensitization) thereby amplifying pain intensity. The magnitude of central sensitization depends on many factors, including the location of the operative site and the extent of the injury.

Postoperative pain may originate in skin, or deeper somatic and visceral structures. It can be divided into nociceptive somatic (from skin, muscles, bones), nociceptive visceral (from organs of the thoracic and abdominal cavity), and neuropathic (caused by damage to neural structures). Usually it is a combination of several types of pain.

2.1.4. Clinical presentation

Acute pain is an unpleasant sensory, emotional and mental sensation (experience) associated with vegetative signs, psychological response and changes in behaviour.

Proper diagnosis of the type and intensity of pain is crucial for an adequate and targeted treatment of acute pain. It requires professional approach in terms of expertise, psychology, and ethics. The patient should feel sufficient empathy on the part of health care professionals. The examination of acute pain should include medical history, physical examination, and specific evaluation of pain.

Pain is an individual and subjective experience, influenced by various physiological and psychological factors, education, prognosis, sleep deprivation, race, gender, and environmental influences. Objective

methods of measuring pain are used more in experimental medicine, and, above all, in chronic pain management (algometer, tail flick test, plantar test, changes in the level of ROS, cholesterol or blood glucose levels). Measuring physiological changes (heart rhythm), response to stress (plasma cortisol), or changes in behaviour (facial expression) can provide important information on the intensity of pain. Other methods of measuring pain are subjective.

The most widely used method of numerical assessment of pain intensity is the visual analogue scale (VAS), where patients specify the intensity of pain by indicating a point along a continuous horizontal line, with numbers from 0 to 10 on the other side. In Numeric Rating Scale (NRS) the patient uses numbers to quantify the intensity of pain – 0 means no pain and 10 corresponds to the worst pain imaginable. In the elderly, NRS is superior to VAS, as these patients understand the numerical scale better. An alternative to numerical scale may be an expanding color circle sector or Faces Pain Scale, which shows facial expressions ranging from the state of well-being to worst pain possible. Acute pain should be routinely monitored in intensive care as well.

2.1.5. Management

The options for pain management are classified on the basis of the administration routes, mechanisms of action, and types of drugs. Oral, intravenous (IV), intramuscular, subcutaneous, rectal, transdermal, intrathecal, and epidural routes are the common routes of administration. Other promising options include neuronal blocks such as neuraxial blocks and peripheral nerve blocks. Some of the advanced techniques for pain management include epidural analgesia (which is efficacious but difficult to manage because it involves the administration of peripheral nerve blocks via catheters) and extended-duration analgesia (which can be administered at home).

The aim of analgesic protocols is not only to reduce pain intensity but also to decrease the incidence of side-effects from analgesic agents and to improve patient comfort (Bonnet 2005). Although opioids remain an important component in managing severe postsurgical pain, their use as the single therapeutic entity causes significant problems such as ventilatory impairment, sedation, nausea and vomiting, and delayed recovery of bowel function. These adverse effects endanger patient safety and/or impair recovery and rehabilitation and thereby delay discharge from hospital. Postoperative pain management practice guidelines and clinical studies endorse the use of a multimodal or balanced approach defined as the use of multiple antinociceptive agents (two or more drugs) with different mechanisms of action. That is, pain is best managed using a combination of methods including regional anesthetic and analgesic techniques (e.g., nerve blocks, local wound infiltrations, epidural catheters) along with systemically administered drugs (Schurr 2004). Generally, a systemic opioid is complemented by one or more adjuvant agents (Meissner 2015). According to IASP and European Pain Federation (EFIC) websites, Systemic analgesics with proven or potential efficacy as components of multimodal analgesia used to treat postsurgical pain include: paracetamol, non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 inhibitors (COX-2), N-methyl-D-aspartate antagonists (ketamine), alpha-2 adrenergic agonists (clonidine, dexmedetomidine), alpha-2-delta receptor modulators (gabapentin, pregabalin), systemic local anesthetics and corticosteroids. Nefopam have also been reported to reduce opioid demand when combined with i.v. morphine PCA (Bonnet 2005).

Patients taking opioids still frequently experience episodes of moderate to severe pain in the first 72 hours after surgery (Apfelbaum 2003). Systemic paracetamol or systemic NSAIDs are also used as part of multimodal therapy in the post-operative setting, often at high daily doses, and are associated with the risk of liver toxicity or renal, gastrointestinal and cardiovascular toxicity, respectively.

Postoperative pain management with locoregional anesthesia techniques is a highly effective solution. According to many studies, these methods are more effective (lower pain score) and at the same time reduce the incidence of adverse effects associated with systemic analgesics.

Local anesthetics can be used in various ways depending on anatomical location and desired effect:

- Infiltration/field block: multiple injections of a local anesthetic are performed around the wound, surgical site, or tissue plain to produce local analgesia;
- Nerve block: nerves in a specific area are targeted with an injection using ultrasound, nerve stimulation, or anatomical guidance.

Bupivacaine HCl is the current standard of care for post-surgical analgesia as one of the long-acting local anaesthetics, but even so it has a limited duration of action after local administration, usually reported as less than 8-12 hours (MARCAIN SmPC 2016).

Alternative local anaesthetic treatment options are needed as part of multimodal therapy to better manage post-surgical pain that offer extended duration and greater magnitude of analgesic effects.

The recognised advantages of multimodal analgesia are the following: improved analgesia, reduced opioids requirements and reduced adverse effects of opioids.

The exact components of effective multimodal therapy vary depending on the patient, setting, and surgical procedure. Clinical practice guidelines on the management of postoperative pain have been published in the USA (Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain 2016;17:131-57). In Europe, recommendations for specific procedures for postoperative pain management are for example proposed by the European Society of Regional Anaesthesia & Pain Therapy and published on its website (https://esraeurope.org/prospect/).

Improved postsurgical or acute pain management contributes to better healing, faster patient mobilization, shortened hospital stays, and reduced healthcare costs. Nevertheless, each technique has its own limitations, and none can achieve complete postoperative pain control. For instance, analgesic techniques such as infiltration of the incision with local anaesthetic solution are associated with a morphine-sparing effect that is limited to a few hours (Bonnet 2005).

Current modalities of postoperative analgesia include surgical site administration and/or nerve block with local anaesthetics combined with the systemic administration of analgesics (multimodal therapy). Multimodal therapy usually includes opioid medications, which have considerable drawbacks including time and resources required for monitoring opioid-related side effects. A reduction in the use of postoperative opioids is desirable to decrease the incidence and severity of opioid-induced adverse effects, such as respiratory depression, nausea, vomiting, constipation, somnolence, pruritus, and urinary retention.

About the product

Zynrelef has been formulated as prolonged-release wound solutions (60 mg / 1.8 mg, 200 mg / 6 mg and 400 mg / 12 mg). The active substances of Zynrelef are bupivacaine and meloxicam, local anaesthesia medicines (amides). Bupivacaine works as a local anaesthetic and meloxicam enhances the efficacy of bupivacaine.

Type of Application and aspects on development

This application has been submitted under Article 10(b) of Directive 2001/83/EC, as amended – relating to applications for new fixed combination products.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as prolonged-release wound solution containing (60 mg + 1.8 mg) / 2.3 mL, (200 mg + 6 mg) / 7 mL, and (400 mg + 12 mg) / 14 mL of bupivacaine and meloxicam respectively as active substances.

Each mL of solution contains 29.25 mg of bupivacaine and 0.88 mg of meloxicam.

Other ingredients are: DETOSU/triethylene glycol/triethylene glycol polyglycolide copolymer, triacetin, dimethyl sulfoxide, and maleic acid.

The product is available:

60 mg bupivacaine/1.8 mg meloxicam: one 10 mL Type I glass vial, 1 vented vial spike, one 3 mL Luer lock syringe, and 1 Luer lock applicator.

200 mg bupivacaine/6 mg meloxicam: one 10 mL Type I glass vial, 1 vented vial spike, one 12 mL Luer lock syringe, and 1 Luer lock applicator.

400 mg bupivacaine/12 mg meloxicam: one 20 mL Type I glass vial, 1 vented vial spike, two 12 mL Luer lock syringes, and 2 Luer lock applicators.

2.2.2. Active Substance

Bupivacaine

General information

The chemical name of the active substance is (*RS*)-1-butyl-*N*-(2,6-dimethylphenyl)piperidine-2-carboxamide corresponding to the molecular formula $C_{18}H_{28}N_2O$. It has a molecular weight of 288.43 g/mol and the following structure:

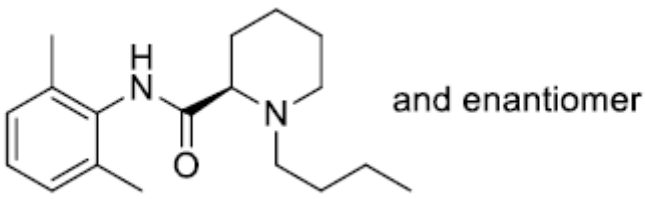


Figure 1: Active substance structure

The chemical structure of active substance was elucidated by a combination of mass spectrometry, NMR spectroscopy, IR spectroscopy, UV-Vis spectroscopy, elemental analysis (CHN) and specific optical

rotation. The solid-state properties of the active substance were measured by melting point, DSC and TGA.

The active substance is a non-hygroscopic white or off-white crystalline powder, crystals or granules. It is soluble in methanol, ethanol and dichloromethane and insoluble in water.

Bupivacaine exhibits stereoisomerism due to the presence of one chiral centre and is manufactured as a racemic mixture. This is routinely controlled in the specifications.

Polymorphism has been observed for the active substance. Two different crystal forms (form 1 and form 2) of bupivacaine base were observed during development and scale-up. These are clearly distinguishable by IR, XRPD and melting point analysis. Form 1 is thermodynamically stable and does not convert to another form during storage. Form 2 was formed at lab scale when the active substance was crystallized from a different solvent and could not be replicated. The melting point is part of the release analysis of bupivacaine base assuring control of formation of Polymorph 1.

Manufacture, characterisation and process controls

Two manufacturers of bupivacaine were initially proposed, but following questions raised by CHMP, one of the active substance manufacturers was withdrawn.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Bupivacaine is synthesized in three main steps using well defined starting materials with acceptable specifications. The choice of proposed starting material is based on ICH Q11 principles.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in double polyethylene bags, which complies with the EC directive 2023/2006 EC and EC 10/2011 as amended.

Specification

The bupivacaine active substance specification includes tests for appearance, identification (IR), optical rotation (Ph. Eur.), loss on drying (Ph. Eur.), bacterial endotoxins (Ph. Eur.), microbiological limits (Ph. Eur.), assay (HPLC), impurities (HPLC), residue of ignition (Ph. Eur.), residual solvents (GC), and water content (KF).

The specifications of the impurities are set according to the requirements in ICH Q3B. The impurity profile is based on the monograph of bupivacaine HCl in Ph Eur.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for impurities testing has been presented.

Batch analysis data (3 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 6 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25ºC / 60% RH) , for up to 12 months under intermediate conditions (30°C/65 %RH and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one batch. One batch of the active substance was stored under stress conditions: high temperature (60°C), high humidity, pH, oxidative degradation (H_2O_2), and 40ºC / 75% RH for oxidation study.

The following parameters were tested*:* appearance, identity, water, chromatographic purity, assay, 2,6-Xylidine, and XRDP. The analytical methods used were the same as for release (except for XRDP, which is not part of the release specification) and were stability indicating.

All tested parameters were within the specifications under long term, accelerated, photostability, and stress conditions. From forced degradation study a formation of 2,6-xylidine has been observed in the light study. The storage conditions should thus include "Protect against light". Bupivacaine base is stable under the conditions investigated and no storage instructions are required.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 48 months protected against light in the proposed container.

<u>Meloxicam</u>

General information

The chemical name of meloxicam is 4-Hydroxy-2-methyl-*N*-(5-methyl-1,3-thiazol-2-yl)-1,1-dioxo-2*H*-1λ^6,2-benzothiazine-3-carboxamide corresponding to the molecular formula $C_{14}H_{13}N_3O_4S_2$. It has a molecular weight of 351.40 g/mol and the following structure:

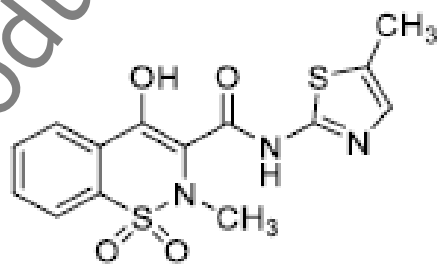


Figure 2: Active substance structure

The active substance meloxicam is described in the Ph.Eur. monograph 01/2017:2373. The manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for meloxicam which has been provided within the current Marketing Authorisation Application.

Information regarding structure and characteristics is provided in the CEP.

Meloxicam is a pale yellow powder practically insoluble in water, soluble in dimethylformamide, very slightly soluble in ethanol.

Meloxicam has a non-chiral molecular structure.

Polymorphism has been observed for meloxicam. Meloxicam is manufactured as a thermodynamically stable crystalline polymorphic Form I.

Manufacture, characterisation and process controls

Two manufacturers of meloxicam were initially proposed by the applicant, but following questions raised by CHMP, one of the active substance manufacturers was withdrawn.

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

The characterisation of the impurities is in accordance with the Ph. Eur. monograph and the EU guideline on chemistry of new active substances.

The active substance is packaged in double polyethylene bags placed in a polyethylene container. Quality and suitability of the primary packaging has been evaluated and considered satisfactory by EDQM.

Specification

The meloxicam release and shelf-life release include appropriate tests and limits for description (visual), identification (IR, HPLC), assay (HPLC and titration), degradation products (HPLC), loss on drying, residue on ignition, residual solvents and microbiological quality (Ph. Eur.).

Satisfactory information regarding the reference standards used for identification, impurities and bacterial endotoxins testing has been presented.

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for bacterial endotoxins and microbial limits. All additional analytical methods have been adequately validated and described according to ICH Q2.

Stability

The stability data have been evaluated by the EDQM. The following re-rest period is mentioned in the CEP: 3 years if stored in double polyethylene bags placed in a polyethylene container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is a prolonged-release (also known as extended release) solution containing a fixed-dose combination of bupivacaine and meloxicam that is intended for single-dose local administration into the surgical site. The finished product is supplied as 4.6 mL and 10 mL presentations filled in a 10 mL vial and an 18.6 mL presentation filled in a 20 mL vial.

The aim of the pharmaceutical development was to develop a prolonged-release formulation for application to a surgical site. It is intended to be applied as a single-dose administration without a needle to coat the affected tissue before the end of surgery and wound closure. The product has been developed to address the unmet medical need for a longer-lasting postoperative analgesic that provides more effective, sustained pain relief.

The finished product is a fixed-ratio combination product that contains two active substances: bupivacaine base and meloxicam, incorporated in a proprietary polymer (AP135).

Bupivacaine and meloxicam both exist in multiple polymorphic forms. Based on fact that both active substances are completely dissolved during the manufacturing process, it is concluded that polymorphism will not affect finished product properties. For the same reason particle size distribution and re-dispersion will not affect finished product properties. The effects due to pH are not applicable in a non-aqueous formulation.

During the manufacture of the finished product, the active substances are first dissolved in dimethyl sulfoxide (DMSO). Therefore, their solubility in mixtures of DMSO and triacetin was investigated at 25°C and 65°C. The concentration of bupivacaine in DMSO during the dissolution step is above its solubility in room temperature. Once fully formulated with AP135, bupivacaine remains in solution, even during storage at 5°C indicating AP135 plays a role in solubilizing the active substance. The amount of meloxicam is well below its solubility in DMSO.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards except for DETOSU/triethylene glycol/triethylene glycol polyglycolide copolymer which is novel excipient used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The viscosity of DMSO-only formulations was too high, so triacetin, an aprotic short chain triglyceride, was added to further reduce the viscosity and facilitate the administration and processing of the formulation.

DETOSU/triethylene glycol/triethylene glycol polyglycolide copolymer is a highly viscous polymeric excipient that provides the slow diffusional release of the active substances over approximately 3 days. After the active substances are released, the polymer undergoes hydrolysis in the aqueous environment leading to small water-soluble products that are rapidly cleared from the body.

No other excipient was tested during the pharmaceutical development to achieve a prolonged release. The choice of this excipient was justified by the fact that "in the case of a viscous polyorthoester, active ingredients are dissolved in the formulation to form a solution with the polymer and solvent excipients and released after administration by diffusion from the depot. Because the mechanism of release is diffusion, the release of active ingredients begins immediately after administration of the formulated drug product. By selecting the appropriate polyorthester polymer compositions, short-term, controlled release over a few days can be achieved. Other commonly used classes of drug delivery polymers, for example poly (ε-caprolactone), poly (lactide acid), and poly (lactic-co-glycolic acid) degrade by bulk erosion and by hydrolysis. As these polymers break down, the encapsulated active ingredient is released. This release mechanism results in a lag phase (ie, the active ingredient is not released for a period of time after administration) during which the polymer must sufficiently hydrolyze to allow the release of active ingredients. A formulation with a lag phase would have an early gap in analgesia. Additionally, erosion of poly (ε-caprolactone), poly (lactide acid), and poly (lactic-co-glycolic acid) polymers is slow, therefore making it impractical to formulate relatively short-release periods on the order of days (3 to 7 days)". Satisfactory information on manufacture, characterization, control, and stability of this novel excipient has been provided.

Formulation development focused on viscosity, dose volume, and achieving sustained simultaneous release of both active ingredients, bupivacaine and meloxicam, while maintaining bupivacaine plasma maximum observed concentration (Cmax) as low as possible.

The compatibility of bupivacaine and meloxicam with each other and with the excipients was evaluated in several forced degradation studies of the finished product. The finished product was exposed to elevated temperature (70°C, ~72 h), and the related substances that were generated were evaluated. There was no degradation of bupivacaine nor were any bupivacaine related substances generated, indicating that the active substances are compatible with one another and bupivacaine is compatible with the excipients.

Initial efforts evaluated the possibility of formulating bupivacaine HCl, but the salt had unacceptably low solubility in solvent excipients that could be used with DETOSU/triethylene glycol/triethylene glycol polyglycolide copolymer. Therefore, the finished product is formulated with bupivacaine base that acts as a "proton sink", becoming protonated as moisture enters the formulation after administration, and therefore reducing the concentration of protons available to hydrolyze the orthoester and controlling the rate of release. In fact, the use of bupivacaine HCl in the formulation, even if it was soluble, would accelerate the rate of DETOSU/triethylene glycol/triethylene glycol polyglycolide copolymer hydrolysis.

In early formulation development, occasional crystallization of the bupivacaine was observed. The addition of an organic acid as a stabilizing agent to prevent crystallization in the formulation was evaluated. The hypothesis was that a small amount of protonated bupivacaine would interfere with the formation of bupivacaine crystals, as it is structurally similar but positively charged, thus disrupting the molecular order needed for crystallization. Of the organic acids screened, only maleic acid was shown to prevent crystallization of bupivacaine in the formulation. After exploration of the excipient ranges, a formulation with an approximately 20-fold lower viscosity than the initial formulation, was developed with half the concentrations of active substances to further increase the volume. This second formulation allowed for easier administration and a sufficient volume to cover large surgical areas. However, the Cmax observed was higher than from the initial formulation indicating a more rapid release of the active substances from the second formulation. Based on the higher observed Cmax, this formulation was discontinued from further clinical evaluation.

In order to achieve a more favorable pharmacokinetic (PK) profile of bupivacaine similar to that from the initial formulation, a third formulation was developed to contain the same percentage by weight of the 2 active substances as the second formulation with the excipient levels adjusted to provide slower release *in vivo*. While the viscosity of this third formulation was slightly higher than in the second formulation, the PK profile for the active ingredients was similar to that of the initial formulation. Therefore, this formulation was selected for phase 2b and phase 3 clinical trials and commercial use.

A customized IVR (*in vitro* release) method was developed based on a forced-air incubator with rotating platform which provided better reproducibility than employing a USP Type 2 apparatus. The customized method consists of placing a depot of finished product in a cylindrical well, with fixed dimensions, that is drilled in a polyoxymethylene insert. The insert is placed at the bottom of a 10-ounce polypropylene specimen container, and phosphate-buffered saline (PBS) is added. The container is closed and placed on the rotating platform of a forced-air incubator calibrated to maintain 37°C ± 0.5°C. At this temperature, > 85% release of both actives is achieved consistently by 72 h, similar to the *in vivo* release profile. Aliquots are withdrawn from a set position within each container at specified timepoints using a manual pipette. These aliquots are analysed for both meloxicam and bupivacaine contents by a validated HPLC assay. The depot size is 200 mg to improve reproducibility, the rotation speed of the incubator platform is 120 rpm for improved mixing, which led to IVR method with good precision and discriminatory power.

A risk assessment of the manufacturing process was conducted to identify critical process steps with corresponding parameters whose variability may potentially have an impact on critical quality attributes (CQAs) of the finished product and should be monitored or controlled to assure the process produces product of desired quality. The risk ranking considered severity, probability and detectability (failure mode and effect analysis (FMEA)). Parameters receiving a risk priority rating high were determined to be critical process parameters.

The finished product quality target product profile (QTPP) was prospectively developed to define design criteria and to form the basis for development of the finished product CQAs. Refer to Table 1 for the QTPP elements, targets, and justifications.

Table 1: Finished Product Quality Target Product Profile

QTPP Element	Target	Justification
Therapeutic Indication	HTX-011 is indicated for application into the surgical site to reduce postoperative pain and the need for opioid analgesics for 72 hours.	Not applicable
Method of Administration	HTX-011 should be administered with the syringe and attached Luer lock applicator (LLA) provided in the HTX-011 kit. HTX-011 is applied into the surgical site following final irrigation and suction and prior to suturing. If multiple tissue layers are involved, apply HTX-011 after irrigation and suction of each layer before closing	Not applicable
Dosing Form	HTX-011 (bupivacaine and meloxicam) extended-release solution is a clear, pale yellow to yellow, viscous liquid	Not applicable
Dosage Strength	HTX-011 contains 29.25 mg/mL bupivacaine and 0.88 mg/mL meloxicam	Not applicable
Dosing Presentations	400 mg and 12 mg in a 20 mL single-dose vial 200 mg and 6 mg in a 10 mL single-dose vial 60 mg and 1.8 mg in a 10 mL single-dose vial	Recommended dose depends on size and anatomical space of the surgical site up to a maximum total dose of 400 mg/12 mg (14.0 mL) for the surgical procedure.

Abbreviations: LLA, Luer lock applicator; RT, room temperature; QTPP, quality target product profile

The proposed commercial manufacturing process parameter ranges for the 50 kg commercial scale were based on evaluation of results from scale-up development studies (0.5 kg laboratory-scale and 20 kg pilot-scale), the manufacture of registration batches and process validation data. The proposed commercial production process utilizes critical process parameters (CPPs) that are identical to the CPPs used for production of pivotal clinical and registration batches.

The finished product cannot be terminally sterilized by heat since meloxicam degrades at high temperatures, nor can it be terminally sterilized by radiation since bupivacaine and meloxicam degrade when irradiated. The finished product is therefore sterilized by sterile filtration.

In the sterile filtration process, the formulated bulk product from the mixing vessel is sterile filtered through two 0.2 µm nylon filters in series by nitrogen pressure into a sterile fill vessel. Throughout the sterile filtration process, due to the sensitivity of DETOSU/triethyleneglycol/triethylene glycol polyglycolide copolymer and the formulation to hydrolysis, moisture is minimized by dry gas blow down and nitrogen purge of equipment before and during use.

Extractables and leachables from the container closure system were evaluated in three studies with different solvents (nitric acid, 10% DMSO, hexane, isopropyl alcohol and cyclohexane). The observed levels of extractables/leachables were determined to be safe.

The finished product is packed in Type I vials which are co-packaged with medical devices intended for the preparation and administration of the finished product. These are a vented vial spike (VVS), which is used to remove the finished product from the vial directly into a syringe, a 3 mL or 12 mL polypropylene Luer lock syringe, and a Luer lock applicator (LLA) which is attached to the syringe for the administration of the product. The medical devices are CE marked. Because the finished product is a viscous solution, the vial is filled with some excess volume that cannot be removed due to hold-up in the vial and device components. Hold-up weights for the syringe and LLA were determined to allow further calculation of the minimal fill volume/weight required for specific doses.

Dose of Zynrelef required depends upon the surgical area of tissue to be treated. Nominal doses based on the formulation and a density of 1.17 g/mL are shown in table below. The nominal volumes shown do not include any hold-up.

Table 2

Bupivacaine (mg)	Meloxicam (mg)	HTX-011* (g)	HTX-011* (mL)
60	1.8	2.40	2.05
200	6	8.00	6.84
400	12	16.00	13.68

*Not including hold up in syringe, LLA, vial or VVS.

The actual volume delivered will be the volume withdrawn minus the hold-up volume in the LLA and the syringe. Therefore, to determine the volume of drug product that must be withdrawn from a vial to deliver the appropriate dose of the formulation, the hold-up in the syringe(s) and LLA(s) was added to the target dose volume. Furthermore, hold-up in vials was added to determine total minimum weight that needs to be filled into vials.

Compatibility studies between the medical devices used for the preparation and administration of the formulation and the finished product were performed by incubating them for varying lengths of time and assessing physical changes in the components as well as the physico-chemical properties of the exposed finished product. Components were exposed to finished product for at least 2 times the anticipated maximum contact time indicated in the SmPC. The product was evaluated for changes in drug content and leachables; in addition, the product was stored for up to 72 hours in syringes and evaluated for changes in viscosity, molecular mass determination (MMD), and in vitro release (IVR) as well. Conversely, the device components were inspected visually for any changes in shape, color, or integrity that may have been associated with exposure to the formulation. There were no detectable observed changes in any of the parameters tested at any time-point.

The compatibility of the finished product with surgical materials was assessed in vitro. Commonly used types of silicone sheets for breast implants, bone cements, metal alloys used in replacement joints, surgical mesh, sutures, and povidone-iodine solution were evaluated to determine either the effect of finished product on the mechanical properties of the material, or the effect of the material on the integrity of the drug product, or both. No major effects were observed when the finished product was in contact with surgical materials

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

The manufacturing process consists of 6 main steps: addition of DETOSU/triethylene glycol/triethylene glycol polyglycolide copolymer, active substance solution preparation, bulk finished product preparation, sterile filtration, aseptic vial filling, and secondary packaging. The process is considered to be a non-standard manufacturing process.

A prospective approach was used for validation of the finished product manufacturing process. Information and experience gained during process development and registration batches production at the commercial scale were used to support the design of the commercial finished product process validation (PPQ). Three commercial scale batches were manufactured to complete the PPQ requirements for each intended commercial fill volume. Validation of the labelling and secondary packaging was completed after demonstrating that 3 consecutive batches meet pre-defined criteria. The same manufacturing process, equipment, and facilities used for PPQ will be used for commercial manufacture. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), dynamic viscosity (Ph. Eur.), water content (KF), molecular mass distribution (GPC), particulate matter (light obscuration), identification of bupivacaine and meloxicam (HPLC, HILIC), bupivacaine assay (HPLC), bupivacaine related substances (HPLC), bupivacaine dose uniformity (Ph. Eur.), meloxicam assay (HPLC), meloxicam related substances (HPLC), meloxicam dose uniformity (Ph. Eur.), *in vitro* release (HPLC), ethylene glycol, diethylene glycol, and dimethyl sulfoxide (GC), triethylene glycol (GC), container closure integrity (dye ingress), bacteria endotoxins (Ph. Eur.), sterility (Ph. Eur.), and extractable volume (Ph. Eur.).

Ethylene glycol (EG) and diethylene glycol (DEG) are organic impurities potentially present in the DETOSU/triethylene glycol/triethylene glycol polyglycolide copolymer. They are tested at release and also monitored on stability, although there are no data to indicate that they are degradation products of formulation components.

The proposed specification limit for EG is below the permissible daily exposure (PDE) in ICH Q3C(R6).

The proposed specification limit for DEG content is supported by results of toxicity study described in scientific literature. Paediatric dosing will be individualized on a weight basis and proportional to adult dosing. Therefore, these acceptance criteria are also suitable for paediatric use.

Triethylene glycol (TEG) is a monomer used in the manufacture of DETOSU/triethylene glycol/triethylene glycol polyglycolide copolymer. Residual monomer is potentially present in the polymer and may also form in the finished product as a hydrolytic degradation product. TEG is monitored on release and stability. TEG, after administration of the formulation in vivo, is released into systemic circulation during polymer hydrolysis and is rapidly excreted. Thus, limits for TEG are set based upon the expected range in production of the copolymer plus the small amounts expected to be generated during storage, and not its toxicological properties.

Control of the polymer content is accomplished by testing the viscosity and MMD of the finished product. Viscosity testing ensures the performance of the product, and Mn and Mw confirm the presence of the polymer.

Control of the triacetin content is accomplished by testing viscosity, IVR, and DMSO content of the finished product. Triacetin constitutes 25.0% of the formulation. A change in the ratio between polymer, DMSO, and triacetin would be observed in viscosity results and IVR release results. Therefore, it is acceptable to omit direct measurement of triacetin content from the finished product specification.

Specific gravity was characterized during product development, and routine control is not considered necessary as the dynamic viscosity controls for appropriate concentration of excipients that determine the specific gravity.

A risk assessment for potential elemental impurities was completed in accordance with ICH Guideline Q3D on Elemental Impurities. Potential sources of elemental impurities evaluated consist of the active substances, excipients, and purified water used in product manufacturing, the finished product manufacturing and packaging equipment used in the finished product production process, as well as the container-closure systems. Based on this assessment, none of the potential sources would introduce elemental impurities into the finished product at levels that exceed the respective ICH Q3D control thresholds. This supports the conclusion that the finished product manufactured using the currently approved procedures, methods, and materials, at the current manufacturing site, meets the ICH Q3D elemental impurity requirements for a parenteral product.

In the context of the on-going review under Article 5(3) of Regulation (EC) No 726/2004 related to the potential presence of nitrosamine impurities in human medicinal products the applicant was requested by CHMP to review his product for potential presence of nitrosamine impurities and to conduct a risk evaluation/risk assessment as appropriate. Risk assessments from the suppliers of the active substances, excipients and finished product manufacturer were provided. Based on the risk assessments provided, the risk of nitrosamine contamination is considered low.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identification, assay, related substances MMD and viscosity testing has been presented.

Batch analysis results are provided for 6 commercial batches of 10- and 20-mL vials confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 commercial scale batches of the 60 mg/1.8 mg, 3 commercial scale batches of the 200 mg/6 mg presentations and 4 commercial scale batches of the 400 mg/12 mg presentation of finished product stored for up to 36 months under long term conditions (5ºC, 25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Stability data from 2 commercial scale batches of 300 mg/9 mg product presentation, which is not currently planned for commercialization, stored for up to 24 months under long term conditions (5ºC, 25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided as supportive information.

Samples were tested for appearance, dynamic viscosity, molecular mass distribution, particulate matter, identification of bupivacaine and meloxicam, bupivacaine and meloxicam assay, bupivacaine and meloxicam related substances, meloxicam dose uniformity, ethylene glycol, diethylene glycol, dimethyl sulfoxide (DMSO), triethylene glycol, in vitro release (IVR) for bupivacaine and meloxicam, container closure integrity, bacterial endotoxin and sterility. The analytical procedures used are stability indicating.

The physicochemical and microbiological characteristics of the finished product remained within the proposed shelf-life specification criteria when stored at long term conditions.

Samples stored at the accelerated storage conditions showed changes expected from an accelerated storage condition. The changes observed are consistent with results seen in samples stored at long term storage conditions.

The stability data for the sideways and upright vial orientations showed that vial orientation made no difference in the product quality. Additionally, stability data from development stability studies with the product presentation of 400 mg/12 mg in a 20 mL vial showed that the desiccant and the Mylar pouch did not have an impact on product quality.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. According to the photostability results a decreasing trend for meloxicam potency, and an increasing trend for meloxicam and bupivacaine related substances have been observed. Therefore, vials should be protected from light and a secondary packaging which provides acceptable protection from UV and visible light was proposed.

A thermal cycling study was conducted to investigate the effects of freeze/thaw cycles on the stability of the finished product. The samples were exposed to a total 72-hour study with cycling occurring during each 24-hour period from -20°C ± 5°C to 40°C/75% RH. All results remained within the proposed commercial specification.

Based on available stability data, the proposed shelf-life of 24 moths and do not store above 25°C. Store in the original package in order to protect from light and moisture. This medicinal product should only be prepared immediately prior to use as stated in the SmPC (section 6.3).

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product and their manufacturing process. However, no design space was claimed for the manufacturing process of the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The active ingredients in HTX-011-56, bupivacaine and meloxicam, are well known. Thus, the focus of the assessment was the combination of bupivacaine and meloxicam in the extended-release formulation.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Study 33-12

The primary aim of the study was to evaluate the analgesic activity of Bupivacaine prepared in unique formulations (HTX02-01 and HTX07-03) with a potential prolonged activity. Bupivacaine was dosed using 2 different routes of administration: instilling (into the wound space) and intra-lesionally (into the margins of the open wound). Instilling administration of HTX02-01 was more active than intra wound administration. HTX02-01 and HTX07-03 had prolonged effect following single administration just before wound closure.

Study 33-13

The aim of the study was to assess the nociceptive activity of various formulations in postoperative pain model in pigs. Treatments with HTX07-1233158; HTX11-1233155 and HTX16-1233159 were active in relieving post operating sensitivity for 6 days. Treatment with HTX11-1233155 was active in completely inhibiting post-operative nociception. Treatment with HTX12-1233153 (containing diclofenac) might have an effect on changing the suture property causing suture fragile.

Study 33-14

The aim of the study was to assess the nociceptive activity of various test item formulations in post-operative pain model in pigs using 2 different methods for test item introduction and different compounds combinations. Treatment with various combination of bupivacaine and meloxicam suggests that the effect of bupivacaine as analgesic agent is more crucial in the mixture than meloxicam in the concentration ranges tested. The results show that the maximum effect of this mixture is already achieved using the combination of 100mg/gm bupivacaine + 7.5mg/gm meloxicam. Comparison between 2 methods of test item introduction suggests that, in this model, the most effective method of administration is by injection under the skin as opposed to laying the test item directly onto the wound bed.

Study 33-24

The aim of the study was to assess the analgesic effect of 5 formulations in the postoperative pain model. Treatment with bupivacaine and meloxicam was more active than the treatment with meloxicam alone. Treatment with bupivacaine and meloxicam at a volume of 3.4 ml was more active than treatment with half concentration or half volume (1.7 ml) suggesting a dose related effect. Treatment with the same bupivacaine and meloxicam concentration using DMSO is more active than using NMP carrier.

Study 33-29

This study was conducted to evaluate the activity of 3 compounds in POP model in the pigs. Treatment with HTX-011-056 resulted in the most prolonged analgesic effect. Treatment with either HTX-011-49,

HTX-011-19 or HTX-011-56 were active in significantly increasing the withdrawal threshold. On study days 3-5, only treatment with HTX-011-056 reached significance vs. saline (15.00±0.00g vs. 4.50±0.50 g for saline group on day 5; $p<0.05$). These data suggest that treatment with HTX-011 formulation was active in increasing mechanical withdrawal threshold. Treatment with HTX-011-56 had the most prolonged activity.

Study 33-61

This study was conducted to evaluate the activity of 3 formulations in POP model in the pigs. All compounds contained bupivacaine at a concentration of 2.5%w/w with different concentration of meloxicam. HTX-11-056 contained the highest concentration of meloxicam (0.075% w/w) compared to HTX-011-062 (0.038% w/w) and HTX-011-063 (0.019% w/w). Treatment with HTX-011-056 resulted in the most prolonged analgesic effect and was more effective than HTX-011-062 or HTX-011-063 with no difference between HTX-011-062 and HTX-011-063. These data suggest that treatment with HTX-011 formulation was active in increasing mechanical withdrawal threshold and had the most prolonged analgesic efficacy. Reducing the concentration of meloxicam below 0.075% w/w significantly affected the analgesic effect of the HTX-011 formulations.

Study 33-68

This study was conducted to evaluate the activity of 3 formulations in POP model in the pigs formulated with 2.5% w/w bupivacaine and with different concentrations of meloxicam: HTX-011-56 (0.075% w/w); HTX- 011-072 (0.1125% w/w); and HTX-011-074 (0.15% w/w). The activity of these formulations was compared to the activity of combined injections of Bupivacaine and Eloxijet (Groups 1 and 2). The effect of treatment with HTX-011-056 (Group 3) or HTX-011-074 (Group 5) was superior to the effect of treatment with Bupivacaine and Eloxijet even when Eloxiject was dosed at a higher dose (6 mg; Group 2). HTX-011-074 was superior to HTX-011-56 and HTX-011-072 in specific time points. Coadministration of bupivacaine HCl and meloxicam (Eloxijet) solutions showed an analgesic effect, which was significantly lower when compared to HTX-011-056. Increasing the concentration of meloxicam from 0.075% w/w to 0.15% w/w (HTX-011-074) significantly increased the analgesic effect when compared to HTX-011-056.

Study 33-71

This study was conducted to evaluate the activity of HTX-002-013 in combination with systematically administered meloxicam (Eloxijet) in POP model in the pigs. Additional aim was to compare the combination activity with HTX-011-074 and HTX-032-001. No statistical difference was found when comparing the activity of HTX-002-013/Eloxiject 6mg (Group 3) with that of HTX-002-013/Eloxiject 3mg (Group 2). Systemic administration of meloxicam (6 mg) with HTX-002-013 (2.5% w/w bupivacaine only formulation) increased the analgesic effect of HTX-002-013 on Days 1 and 2 with no difference on Day 3 to Day 6. Effect of HTX-032-001, a formulation with both bupivacaine (0.5% w/w) and meloxicam (0.15% w/w) was no different that HTX-002-013. HTX-011-074 (2.5% w/w bupivacaine and 0.15% w/w meloxicam) was significantly more effective that HTX-002-13 with and without systemically administered meloxicam (6 mg) and HTX-032-001. The most active formulation was HTX-011-074.

Study 33-87

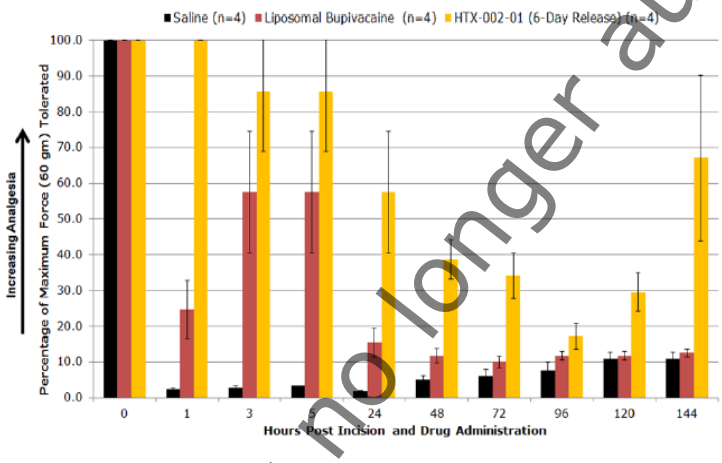
The objective of this study was to investigate the effects of a sustained release formulation of bupivacaine and meloxicam (HTX-011-056) or saline on incisional pH in the pig. A pig incisional model was developed to assess pH changes in a surgical incision. pH measurements were collected in the tissues surrounding a surgical incision made on the dorsum of the pig. In saline treated or sham control incisions, a decrease in pH occurred soon after the incision was made, and the lower pH was maintained for at least 48 hours. Treatment of incisions with HTX-011-056 created an environment surrounding incision allowing for incisional pH to return to a normal pH (baseline) within 24 hours.

Results analysis

a) Assessment of the analgesic efficacy of an extended-release formulation of bupivacaine alone and liposomal bupivacaine (Study 33-12, Study 33-14).

BPV contained in their design polymer offers a higher efficacy at all the timepoints in comparison with liposomal BPV such as Exparel®. It was concluded that "administration of HTX-002-01 resulted in a greater analgesic effect compared with liposomal bupivacaine through 144 hours (see Fig 3). The analgesic effect diminished for HTX-002-01 from 48 to 96 hours and for liposomal bupivacaine from 24 hours".

Figure 3: Analgesic Effect of an Extended-Release Formulation of Bupivacaine Alone and Liposomal Bupivacaine



Conclusions made by the applicant are questionable since the applicant has not selected Exparel with the highest dosage. Indeed, a formulation with 266 mg of BPV in Exparel would have been a better comparator since the analgesic effect relies on BPV and therefore local available concentrations may deeply affect the scores obtained. Therefore, the applicant was asked to discuss why Exparel with the lowest concentration (106.4 mg) in BPV was chosen as the comparator. The applicant has underlined that the purposes of studies with HTX-002-001 (extended-release formulation of BPV) and Exparel (liposomal BPV) were not to demonstrate superiority of HTX-002-001 over Exparel. Doses selected were based on time of release and length of the incision. It is agreed that loss of analgesia is expected after time, however it is not clearly understandable how strong analgesia with HTX-002-01 (BPV only) could occur after 1 hr post incision and drug administration.

Moreover, no information regarding local concentrations and kinetic of release from HTX-002-01 and Exparel are available and due to the difference of nature between the two products (liposome vs polymer) the use of Exparel is questionable. The applicant answered that differences observed regarding PK profile are related to the kinetic release of BPV and the amount of BPV released at the site of administration is similar between HTX-002-01 and Exparel. In addition, it appears in Fig 3 that a full analgesia is observed 1hr post dose with HTX-002-01 whereas an efficiency of only 20% is observed with Exparel at the same timepoint. It appears also from Fig 3 that analgesic effect with HTX-002-01 drops from 5 to 96 hrs, however superiority vs Exparel is not demonstrated at that timepoint. Superiority of HTX-002-01 over Exparel has been observed until 72 hrs. Nevertheless, it is difficult to conclude that the superiority is correlated with the nature of the product of the highest total BPV concentration. In addition, it is not clear whether or not the full analgesia observed at 1hr is due to a burst release of BPV from HTX-002-01. Overall, plasma concentrations observed in BPV only describe systemic exposure and cannot describe the release of the chemical substance from its support and the mean residence time. It is not possible

to correlate what is observed in systemic (quick massive release in BPV?) moreover the applicant has stated that measurement of the local tissue concentration of bupivacaine following administration of HTX-002-01 (extended-release formulation of bupivacaine) or Exparel (liposomal bupivacaine) is not possible.

In addition, a further increase in analgesia was observed at 144 hrs whereas no return was observed for Exparel and the applicant did conclude: "As inflammation subsides with time, the pH at the incision returns to physiologic pH and more bupivacaine in the un-ionized lipid-soluble form is available to penetrate the nerve membrane. This could explain the return of the analgesic effect of HTX- 002-01 at around 120 hours." In theory similar finding could be observed if sufficient local concentration of BPV is available whatever the origin of the product.

Overall superiority of HTX-002-01 over Exparel (106.4 mg) is only partially demonstrated although the highest efficacy for Exparel was observed only between 3-5 hrs.

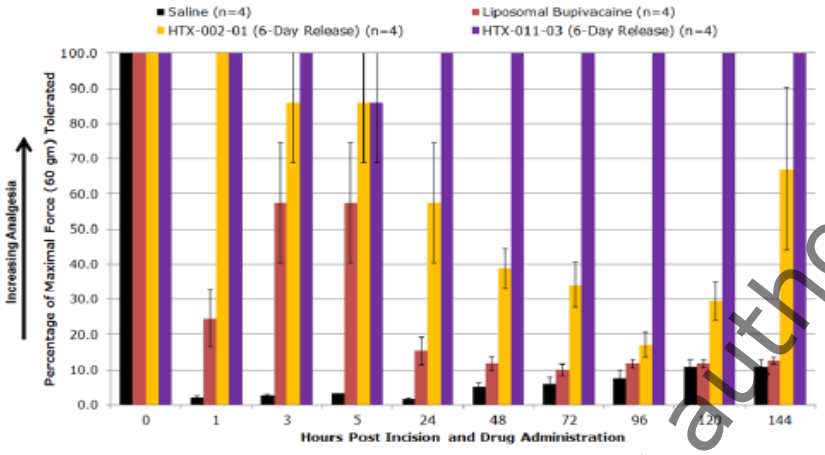
b) Assessment of the analgesic efficacy of the extended-release combination formulation of bupivacaine and meloxicam (Study 33-12, Study 33-13, Study 33-14).

The reduced sensitivity in the VF test was expressed as an increase in the withdrawal force and therefore reflecting the analgesic effect of the test article. The applicant has highlighted that compared to saline and as expected a significant beneficial effect following instilling dosing of various extended-release formulations, containing ropivacaine or BPV, versus vehicle was observed during the study. Best scores were obtained after 6 days for G5 and G6, however score obtained in G6 should be tempered based on the presence of buprenorphine (analgesic effect).

The applicant has stated that "Meloxicam demonstrated the optimal profile of potency (to allow a practical dose for incorporation in the matrix) and other physicochemical properties, such as solubility, for use in combination with bupivacaine formulated with the TEG-POE polymer." However, there is no clear demonstration how MLX was the perfect candidate compare with other NSAID and since local pH variation is the key factor why a standard pH modulator has not been used. In other words, there is no proper demonstration that MLX acts as an active substance, in that case MLX would be equivalent to an excipient and the product may not rely on the EMA/CHMP/158268/2017 guideline on fixed combination medical.

The applicant has compared the analgesic potency of HTX-002-01 (BPV 316 mg), HTX-011-03 (BPV 351 mg / MLX 81.9 mg) and Exparel (BPV 106.4 mg) over saline test article. Saline, HTX-002-01, and HTX-011-03 were administered by instillation, and liposomal bupivacaine was administered by injection in each side of the wound. Increasing analgesia scores of the various test articles are reported in Fig 4. HTX-002-01 is an extended-release formulation of bupivacaine alone designed to release bupivacaine for 144 hours. HTX-011-03 is an extended-release combination formulation of bupivacaine and meloxicam designed to release bupivacaine and meloxicam for 144 hours. Liposomal bupivacaine was designed to release bupivacaine for up to 96 hours.

Figure 4: Analgesic effect of an extended-release combination formulation of bupivacaine and meloxicam, extended-release formulation of bupivacaine alone, and liposomal bupivacaine



The choice of the concentration of BPV in Exparel is questionable in order to compare the nociceptive activity of various formulations in this animal model. Scores obtained for HTX-002-01 and Exparel have been previously discussed. From Fig 4 it appears that full analgesia was obtained from 1hr pots administration till 144 hrs without any drop of the effect. These results seem to demonstrate that addition of MLX to BPV led to a higher effect or did maintain the effect at the same level for a long period. Therefore, from that aspect potency of HTX-011-03 > HTX-002-01 > Exparel and has shown a "synergistic activity" of the combination. As previously hypothesized, full analgesia at 1hr pots administration is the result of a "burst effect" releasing locally BPV. Nevertheless, the full potency for HTX-011-03 observed during almost all the timepoints is questionable since it is not known if that potency is directly linked to the "synergistic activity" or related to the high dose level of MLX involved. Thus, the choice of a high dose in MLX (81.9 mg) is debatable since this dose is by far superior to the highest dose used in humans (15 mg/day). 81.9 mg in MLX for a mini pig of 40 kg would correspond to a human dose of 116 mg based on a human of 60 kg. Overall, superiority of HTX-011-03 over HTX-002-01 is only partially demonstrated. The applicant was asked to discuss the rationale for the dose selection in MLX used in HTX-011-03. The applicant did justify the use of a high dose of MLX in the context of sustained-release. This was considered acceptable. Nevertheless, there is no indication based on PK data that the effective daily release of MLX and how closed it is to the maximum daily oral dose in humans (15 mg/day). It is not clear why a strong analgesia is observed so quickly whatever the formulation used and less is known regarding the minimum effective local concentration in BPV (released from the polymer) to have a pharmacological effect on pain release. In addition, it is observed that combination with MLX results in higher efficacy.

c) Administration of bupivacaine and meloxicam in the extended-release combination formulation results in a greater analgesic efficacy than bupivacaine alone or meloxicam alone in the extended-release formulations (Study 33-12, Study 33-14 and 33-24).

Treatment with bupivacaine and meloxicam was more active than the treatment with meloxicam alone.

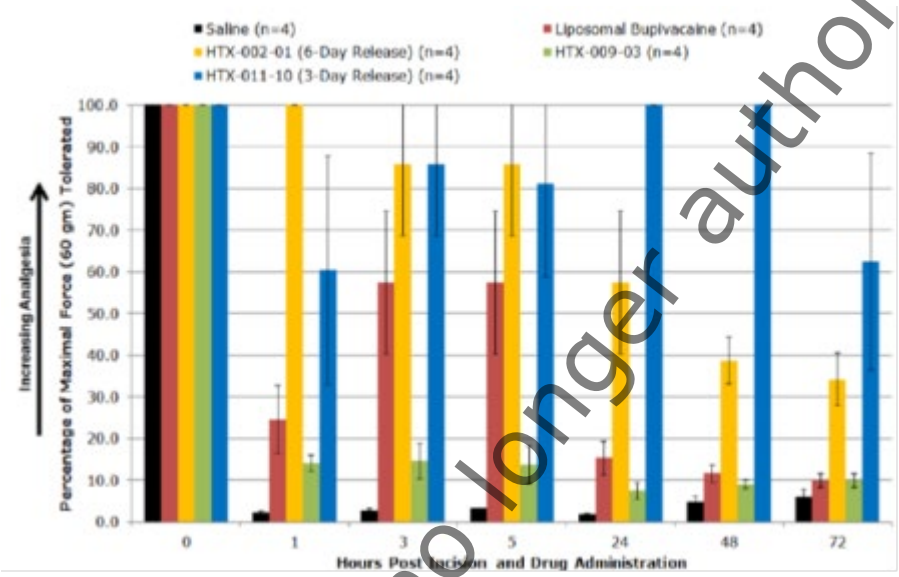
Treatment with bupivacaine and meloxicam at a volume of 3.4 ml was more active than treatment with half concentration or half volume (1.7 ml) suggesting a dose related effect.

Treatment with the same bupivacaine and meloxicam concentration using DMSO is more active than using NMP carrier.

Based on results obtained from studies 33-12, 33-14 and 33-24, the applicant has compared the analgesic effects of HTX-002-01 (BPV 316 mg), HTX-011-10 (BPV 234 mg / MLX 8.9 mg), HTX-009-003

(MLX 3 mg) and liposomal BPV Exparel (106.4 mg). HTX-002-01 is an extended-release formulation of BPV alone designed to release BPV for 144 hours. HTX-009-03 is an extended-release formulation of MLX alone designed to release MLX for 72 hours. HTX-011-10 is an extended-release combination formulation of BPV and MLX designed to release BPV and MLX for 72 hours. Liposomal bupivacaine was designed to release BPV for up to 96 hours.

Figure 5: Analgesic effect of extended-release formulations of bupivacaine alone or meloxicam alone, extended-release combination formulation of bupivacaine and meloxicam, or liposomal bupivacaine



The applicant stated that "local administration of an extended-release combination formulation of bupivacaine and meloxicam results in greater and longer analgesic efficacy compared with local administration of extended-release formulations of each individual active ingredient alone."

The choice of the concentration of BPV in Exparel is questionable in order to compare the nociceptive activity of various formulations in this animal model. From Fig 5 it appears that similar efficacy between HTX-002-01 and HTX-011-10 is observed at 3-5 hrs post incision corresponding to the maximum efficacy of Exparel with an overall lower effect compared with those from HTX-002-01 and HTX-011-10. Analgesic effect of HTX-002-01 dropped after 24 hrs whereas analgesic effect reached its maximum for HTX-011-10. Therefore, superiority of HTX-011-10 over HTX-002-01 was demonstrated between 24-48 hrs. Nevertheless, based on the high SD observed at 72 hrs for HTX-011-10, superiority of HTX-011-10 over HTX-002-01 was less pronounced. Since HTX-002-01 was designed to release BPV for 144 hrs and HTX-011-10 was designed to release BPV and MLX for 72 hours, it would have been interesting to follow the analgesic effect over 144 hrs. Regarding HTX-009-03, analgesia scores were the lowest observed throughout all the time-period demonstrating that MLX alone was not sufficient to provide a satisfying analgesic effect.

Overall, it can be concluded that local administration of extended-release formulation of BPV and MLX (HTX-011-10) was more efficient than extended-release formulation of BPV (HTX-002-01) between 24-48 hrs with the same tendency up to 72 hrs. Therefore, MLX seemed to prolong the analgesic efficacy of BPV after 24 hrs. Based on these results and scores obtained up to 24 hrs pots incision, it appears that release of BPV and MLX or time residency at the local site of administration were different. A question was raised if there a real extended-release for both substances or if real extended-release is observed solely for MLX. The applicant has answered that the same TEG-POE polymer is used to achieve the

extended release in all HTX-002 and HTX-011 (and HTX-009, meloxicam only) formulations tested in nonclinical and clinical studies including HTX-011-56, the intended commercial formulation tested in Phase 2b and Phase 3 clinical studies. PK and/or in vitro release (IVR) profiles have been used to demonstrate the extended release of bupivacaine and meloxicam from HTX-011 and bupivacaine from HTX-002 for several formulations as well as meloxicam from HTX-009. Applicant's response underlined that both polymers were not designed to release BPV over the same length period. The applicant has acknowledged that although no PK data are available for HTW-011-10, IVR profile was submitted of both active ingredients BPV and MLX. The applicant has considered similar profiles for both compounds nevertheless the extended release for MLX appeared more delayed in comparison with BPV. Whereas the applicant has considered that BPV PK profile is not modified by MLX presence (see Figure 5), both polymers were not designed to release BPV over the same period. Based on Figure 5, it cannot be concluded that difference in PK profile between BPV and MLX is due to MLX clearance. Indeed, it appears that MLX release seems to be delayed but it is unknown how valuable could be the in vitro/in vivo correlation. In addition, as previously mentioned, real description of the PK profile of Zynrelef is difficult to figure out since only a part of the process is observed (after systemic passage). In conclusion, extended release is observed for BPV and MLX, however PK profile cannot be considered similar and MLX's release from the matrix appears more delayed. Uncertainties remain regarding the whole PK process and no translation to Human can be drawn. Superiority of BPV: MLX extended-release over BPV only extended-release is significant between 24-48 hrs post incision.

d) Determination of the lowest effective Meloxicam: Bupivacaine ratio in an extended-release formulation

In Study 33-61, treatment with HTX-011-056 has resulted in the most prolonged analgesic effect and was more effective than HTX-011-062 or HTX-011-063 (no difference between HTX-011-062 and HTX-011-063). All compounds contained BPV at a concentration of 2.5%w/w with different concentration of MLX. HTX-11-056 contained the highest concentration of MLX (0.075% w/w) compared to HTX-011-062 (0.038% w/w) and HTX-011-063 (0.019% w/w). Therefore, Study 33-61 has highlighted that a dose increase in MLX will enhance efficacy. In addition, increase in MLX concentration has also been associated with a raise in efficacy at Day 4 with a maximum observed at Day 5 for HTX-011-56 in comparison with HTX-011-062 and HTX-011-063. The applicant was expected to explain why HTX-011-56 profile is different after Day 4 whereas similarity was observed for HTX-011-62 and HTX-011-63. The applicant did justify discrepancies due to abnormal response from Animal 28. The answer provided was endorsed.

In Study 33-68:

- Superiority of treatment was observed with HTX-011-056 (Group 3) or HTX-011-074 (Group 5) vs Bupivacaine and Eloxijet even when Eloxiject was dosed at a higher dose (6 mg; Group 2). Coadministration of bupivacaine HCl and meloxicam (Eloxijet) solutions showed an analgesic effect, which significantly lower, when compared to HTX-011-056. Increasing the concentration of meloxicam from 0.075% w/w to 0.15% w/w (HTX-011-074) significantly increased the analgesic effect when compared to HTX-011-056. It appears that superiority of HTX-011-074 was observed over HTX-011-56 and HTX-011-072 in specific time points. Therefore, the applicant was expected to discuss why formulation HTX-011-074 was not selected as the final formulation instead of HTX-011-56. The applicant justifies the development of HTX-011-56 based on its lowest effective MLX:BPV ratio in the extended-release combination formulation. This is acknowledged, also in light of the results obtained in clinical studies.

No dose-response relationship (trend of effect of HTX-011-072 always reduced compared to HTX-011-56) in the mean von Frey force required for withdrawal. A question was raised on how this be justified in light of the rationale proposed behind the use of such combination therapy. The applicant presented the relationship between the average von Frey withdrawal force and the MLX:BPV ratio. A clear dose

(MLX:BPV ratio) response with increasing amounts of meloxicam can be extrapolated. These data further justify the choice of developing HTX-011-56, which presents the lowest effective MLX:BPV ratio in the extended-release combination formulation.

e) Systemic administration of meloxicam does not enhance analgesic efficacy of locally administered bupivacaine alone in the extended-release formulation

Conclusion of the applicant claiming superiority of HTX-011-56 over HTX-002-13 could be accepted until 24 hrs and after 48 hrs even though high variability has been observed. Returns in analgesia profile is observed but this phenomenon was not explained.

f) Determination of a potential mechanism by which meloxicam enhances the analgesic efficacy of bupivacaine

Study 33-87 should be considered as the key study to justify the use of MLX regarding the effect on pH variation. A drop of pH was only observed on the intra-dermal area whereas no drop was observed on the intra-incisional area. In addition, discrepancy is observed wherein raise in pH is observed when HTX-011-56 is used. Indeed, if a raise in pH is observed after a drop due to incision, it would have been observed at the intradermal interface, therefore the raise described would correspond to the intradermal part. However, HTX-011-56 would be applied below the skin incision (intra-incisional) where no drop in pH was observed therefore the use of MLX as pH modulator is confusing and should be discussed by the applicant. The applicant has stated that: "*the Agency' s interpretation of Figure 2 in Study Report 33-87 is correct: a drop in the pH was observed in the intradermal tissues surrounding the incision and not inside the intraincisional pocket formed by the incision. The pH in the intraincisional pocket does not decrease because the mechanism of pH drop (vasoconstriction and infiltration and activation of neutrophils) occurs within the tissues (details are described in the response to the Major Objection #264)*". The applicant has acknowledged that Section 2.6.2.2.1.3 and related descriptions in the text are not clear. Rise in the pH is observed in the intradermal tissues surrounding the incision due to MLX presence via diffusion. However, less is known regarding local concentrations in MLX and time residency at this interface and no reply would be given by the applicant and therefore the issue was not pursued. In addition, PK results generated in pigs have shown a similar PK profile between BPV and MLX, whereas significant differences were observed in dogs and rats species.

Secondary pharmacodynamic studies

No secondary pharmacology studies were conducted.

Safety pharmacology programme

The applicant conducted hERG test with MLX that was in principle not in accordance with the regulatory standards. However, IC_{20} inhibition of hERG would correspond to a circulation concentration in MLX of 10 000 ng/mL whereas C_{max} observed at the MHRD (BPV 400 mg/ MLX 12 mg) was measured between 270-527 ng/mL. Moreover, Cmax values are 4-fold lower than the mean C_{max} measured with the lowest approved oral dose of MLX (MOBIC 7.5 mg/day), no effects on ECGs were observed during repeated-dose toxicity studies and no effect on QT was observed in clinic. Overall, the effects on CV can be considered as potentially low.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies were conducted.

2.3.3. Pharmacokinetics

The following studies were conducted:

- 2 absorption studies with HTX-011-56 in rats (study 33-79) and dogs (33-36).
- 1 excretion study with HTX-011-56 in minipigs (study 33-77).
- 1 PK drug interaction study with HTX-011-56 and lidocaine in minipigs (33-78).
- 2 other PK studies with bupivacaine alone and meloxicam alone in extended-release formulations in dogs (study 33-47 and study 33-69).

In the absorption studies, exposure to bupivacaine and meloxicam following administration of HTX-011-56 was assessed in rats and dogs following a single subcutaneous administration.

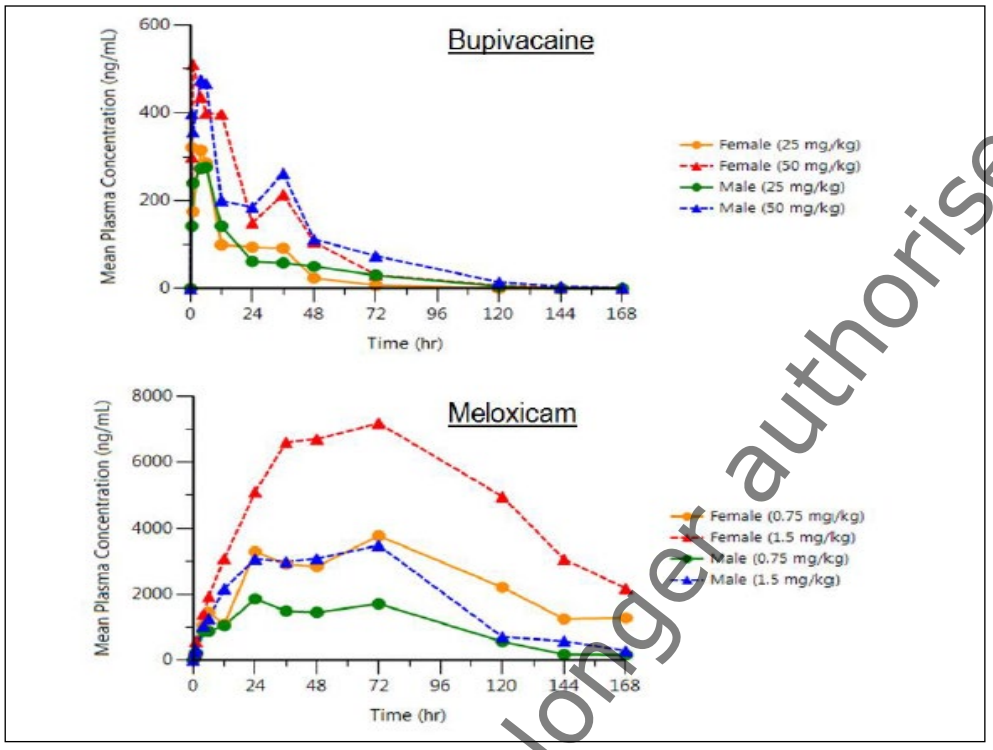
In Study 33-79 male and female rats (9/sex/group) were administered as a single SC dose HTX-011-56 at a low (25 mg/kg bupivacaine and 0.75 mg/kg meloxicam) or a high (50 mg/kg bupivacaine and 1.5 mg/kg meloxicam) dose level.

Table 3: Mean PK parameters for bupivacaine and meloxicam in SD rats following a single SC administration of HTX-011-56 (Study 33-79)

Dose of HTX-011-56 (mg/kg)	Analyte	Sex	N	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{inf} (h·ng/mL)
Low dose							
25	Bupivacaine	M	9	20.8	6.00	276	7,260
		F	9	13.6	0.50	321	6,240
0.75	Meloxicam	M	9	26.3	24.00	1,860	175,000
		F	9	NC[a]	72.00	3,770	NC[a]
High dose							
50	Bupivacaine	M	9	18.1	4.00	474	16,400
		F	9	16.2	1.00	510	15,000
1.5	Meloxicam	M	9	36.5	72.00	3,480	340,000
		F	9	40.5	72.00	7,180	962,000

[a] Not calculated due to insufficient number of samples.

Figure 6: Mean concentration-time profiles of bupivacaine and meloxicam in SD rats following a single SC administration of HTX-011-56 (Study 33-79)



In Study 33-36, male and female Beagle dogs (5/sex/group) were administered a single SC dose of HTX-011-56 (6.96 mg/kg bupivacaine and 0.209 mg/kg meloxicam for males and 6.66 mg/kg bupivacaine and 0.200 mg/kg meloxicam for females).

The objectives of the Study 33-77 were to measure levels of the primary hydrolysis products triethylene glycol (TEG), pentaerythritol monopropionate (PEMPA), pentaerythritol (PE), the metabolite triethylene glycol monocarboxylic acid (TEG acid), bupivacaine (BPV), and meloxicam (MLX) in the plasma, milk, and urine of nursing sows following a SC dose of HTX-011-56 within 48 hours of farrowing, and to measure levels of TEG, PEMPA, PE, TEG acid, BPV, and MLX in the plasma, and urine of piglets following dosing to the sows.

The aim of Study 33-78 was to determine the PK profiles of BPV and MLX after a single administration of HTX-011 to a 5 cm incision with or without lidocaine in naïve male Yucatan minipigs (12 animals: 3 / group). Lidocaine co-administration with HTX-011-56 did not result in any significant modification of the individual PK parameters of BPV and MLX.

In Study 33-47 (Study Report 33-47), male and female dogs (5/sex/group) were administered a single SC dose of bupivacaine alone in an extended-release formulation HTX-002-13 wherein HTX-002-13 contains the same amount of bupivacaine as HTX-011-56.

In Study 33-69 (Study Report 33-69), male and female dogs (5/sex/group) were administered a single SC dose of meloxicam alone in an extended-release formulation (HTX-009-05). HTX-009-05 contains the same amount of meloxicam as HTX-011-56.

The distribution and excretion of the TEG-POE polymer in HTX-011-56 were evaluated during the development of United States (US)-approved parenteral product, SUSTOL® (granisetron) extended-release injection, for subcutaneous use. SUSTOL is formulated with vehicle, APF18A, which is composed of 80% TEG-POE polymer and 20% methoxypolyethylene glycol (MPEG)-550.

In the development of SUSTOL, the TEG-POE polymer was assessed following SC local administration consistent with the Food and Drug Administration (FDA) *Guidance for Industry on Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients* (May 2005) and Committee for Medicinal Products for Human Use (CHMP) *Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product* (EMEA/CHMP/QWP/396951/2006, June 2007).

To assess the distribution and excretion of the TEG-POE polymer in APF18A, the TEG moiety was randomly labeled throughout the molecule. Thus, the results of these assessments provide information on the distribution and excretion of the TEG-POE polymer in HTX-011-56.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies did not reveal any systemic toxicity. No deaths were recorded, no effect on food consumption, body weight, urinalysis parameters, on coagulation, on haematological parameters… were observed. The main observed effects were localised at the injection site and clinical signs observed consist mainly in crust, lesions, and skin discoloration. Microscopic findings at the dosing site corresponded to minimal to moderate SC necrosis, inflammation, oedema, epidermal erosive/ulcerative inflammation. Overall, all the test articles were well tolerated and TK analysis have highlighted exposure to all tested animals.

Repeat dose toxicity

Repeated-dose toxicity studies with up to a 15-day observation period were conducted in SD rats or beagle dogs with the aim to assess systemic and local toxicity of HTX-011-56 under exaggerated conditions. No mortalities were observed during both studies and no findings suggestive of systemic toxicity. In rats (study 33-85), similar non-adverse inflammatory findings were observed following administration of HTX-024-02 or HTX-011-56 at the dosing sites as in the single-dose studies nevertheless incidence and severity were higher compared to single dose toxicity studies. Full recovery of the inflammatory changes was almost observed at the end of the observation period. In dogs (study 33-86), adverse findings were observed in animals (except saline group). In animals administered HTX-024-02, moderate to severe oedema and hypoactivity, dermal scabs, and swollen sites were present and serosanguinous fluid at the dosing sites of some animals were noticed. Decreases in body weights and changes in clinical pathology parameters were linked with acute inflammatory reaction to HTX-024-02. Based on these events, dose volume for HTX-024-02 was decreased from 1 mL/kg to 0.5 mL/kg. Overall, HTX-011-56 was well tolerated and no systemic toxicity was observed.

Supportive data with TEG-POE polymer

Nonclinical toxicology studies of APF18A were conducted in the development of the US-approved parenteral product, SUSTOL. Because APF18A is composed of 80% TEG-POE polymer, the nonclinical toxicology studies conducted with APF18A administered SC are relevant to the assessment of safety of the TEG-POE polymer in HTX-011-56.

The TEG-POE polymer has been qualified in:

- 2 GLP repeated-dose toxicity studies in rats and dogs;
- 2 GLP in vitro genotoxicity studies + 1 GLP in vivo genotoxicity study in rats

- 4 GLP Segments 1 through 3 reproductive and developmental toxicity studies in rats and rabbits that evaluated APF18A.

The results of the repeated-dose studies of APF18A were consistent with those conducted in the development of HTX-011-56.

- No systemic toxicity.
- At the dosing sites, transient inflammatory changes.
- No genotoxic potential
- No reproductive and developmental toxicity of the TEG-POE polymer.

Genotoxicity

An Ames test was conducted in accordance with OECD guideline with a product derived form HTX-011-15 wherein relative BPV and MLX concentrations are higher, 4-fold and 20-fold respectively. In presence and/or absence or S9 metabolic activation system no significant increase in the number of revertant colonies was observed and therefore it was concluded that HTX-011-15 was not genotoxic and by analogy HTX-011-56 as well. In addition, the applicant has submitted results of genotoxicity studies conducted on APF18A polymer that should support the use of the TEG-POE polymer in HTX-011-56. Applicant was expected to discuss why the standard genotoxicity test battery is not needed. Applicant's response was based on previous results regarding BPV and MLX. Concerning the evaluation of the genotoxic potential of TEG-POE, the applicant relied on *in vitro* data (mutagenicity item) and in vivo data (rat μnucleus). Moreover, the applicant has justified the lack of standard genotoxicity test battery for HTX-011-56 since an Ames test was performed with HTX-011-15 which contains higher concentrations of MLX, BPV and TEG-POE. In addition, genotoxicity testing was in line with CHMP Guideline for the non-clinical development of fixed combinations of medicinal products (CHMP/SWP/258498/05; January 2008) and ICH M3(R2).

Carcinogenicity

No carcinogenicity studies were conducted.

Reproduction Toxicity

Reproductive and developmental toxicity studies were not conducted. Relevant data is already available from product information for already approved medicinal products containing bupivacaine and meloxicam.

Local Tolerance

Local tolerance was assessed in 6 GLP studies

Study 33-83

Single SC administration of HTX-011-56 in a surgical bone defect model was clinically well-tolerated. No differences in bone in-growth or regeneration of the adipose and hematopoietic tissue when compared to untreated or saline-treated limbs. The NOEL was set to 45.4 mg/kg BPV with 1.37 mg/kg MLX.

Study 33-80

Findings observed (surgical site skin bruising, discoloration, swelling) were procedure-related and moderate erythema and oedema were observed on the surgical site. No differences between control and test groups for any of the three types of meshes, were observed. No treatment-related biological changes for any of the three types of mesh implantation. All pathology findings were comparable regardless of the type of surgical mesh. This study has demonstrated that single administration of HTX-011-56 with implantation of surgical meshes Gore-Tex, polypropylene, or polyester was biocompatible and tolerable. No adverse impact on the integrity of the tested meshes after implantation up to 14 days were noted.

Study 33-41

No increase in incidence or severity of the dermal and/or subcutaneous changes indicative of normal and comparable reparative process at incision sites after administration of all three tested items compared to the control (saline and vehicle) and comparator (HTX-002-014). No difference in healing between test items and the comparator and the changes observed were considered to be related to the normal process of healing.

Study 33-54

BPV/ MLX induced a slightly increased incidence of the findings but these changes were apparent at a low incidence. Minimal differences of incidence and severity of the dermal and/or subcutaneous changes were observed across all controls, BPV and MLX incision sites indicative of comparable reparation.

Study 33-42

Single administration of HTX-024-001 Vehicle Control, HTX-002-14, HTX-011-49, or HTX-011-56 as a brachial plexus block in dogs was well tolerated with no adverse findings evident 3 or 14 days following administration.

Study 33-63

Perineural administration to male beagle dogs of HTX-011-056 and bupivacaine HCl (reference) for 3 consecutive days, were well tolerated. Anaesthetic properties of HTX-011-056 were demonstrated, but there was no indication of prolonged effects when compared to bupivacaine HCl. There were no gross or microscopic changes related to HTX-011-056 or bupivacaine HCl were noticed. Higher C_{last} confirmed the extended kinetics of HTX-011-056 when compared to bupivacaine HCl.

2.3.5. Ecotoxicity/environmental risk assessment

The applicant has submitted a justification for the absence of a complete Environmental Risk Assessment (ERA) for bupivacaine in the marketing authorization application (MAA) for Zynrelef (bupivacaine and meloxicam) prolonged-release wound solution. A separate ERA document has been prepared for meloxicam.

The justification for the absence of a complete ERA for bupivacaine is on the basis that it is already utilized in a variety of approved drug products and Zynrelef is intended to replace the use of already existing bupivacaine-containing drugs at a same or lower dosage, thereby not significantly increasing the overall environmental exposure of the active ingredient, bupivacaine. The absence of significant increase of the environmental exposure is furthermore demonstrated by comparing the recent bupivacaine EU consumption data with the expected production volume for Zynrelef.

From meloxicam ERA assessment it appears that the logDow value of meloxicam is below 3 (i.e., logDow = 1.6 at pH 5, 0.1 at pH 7 and -0.5 at pH 9). Therefore, it is not identified as a PBT or a vPvB substance.

The Phase I PECSW of meloxicam (0.00049 µg/L) does not exceed the action limit of 0.01 µg/L, and meloxicam is not expected to affect the reproduction of vertebrate or lower animals at concentrations lower than the action limit of 0.01 µg/L. A Phase II environmental fate and effects assessment is thus not triggered.

2.3.6. Discussion on non-clinical aspects

The applicant has submitted a pharmacological package based on experiments performed in piglets wherein POP in pigs was chosen as the animal model. POP in pigs is a usual model and therefore it is acceptable to demonstrate the POC of HTX-011-56 in this model. The aim of these studies was to demonstrate the analgesic efficacy of locally administrated extended-release formulation of BPV and MLX. Main claim of efficacy is based on the use of low dose of MLX in the formulation in order to normalize the local pH of the acid environment (caused by the incision) and therefore modify the ratio between ionized: un-ionized form of BPV. Only the un-ionized form is able to penetrate into the nerves and thereby enabling analgesic activity. Overall, the elements presented to support the POC needed clarifications since some discrepancies have been noticed in the interpretation of the studies conducted. Indeed, the main question mark relies on the pH variation at the site of administration wherein from data submitted no pH drop was observed in study 33-87 and therefore the necessity of use of MLX was questioned.

Prior to that, the applicant has attempted to demonstrate the superiority of an extended formulation of BPV alone (HTX-002-1) over liposomal BPV, but the choice of that comparator in terms of BPV concentrations was not optimal. Thus, overall superiority of HTX-002 could be considered as partially demonstrated.

The applicant has studied the analgesic efficacy of the extended-release combination formulation of BPV and MLX in studies 33-12, 33-13 and 33-14. The results generated demonstrate that that addition of MLX to BPV led to a higher effect or did maintain the effect at the same level for a long period. Therefore, from that aspect potency of HTX-011-03 > HTX-002-01 (BPV only)> Exparel and has shown a "synergistic activity" of the combination. Nevertheless, since very high concentration of MLX was used in HTX-011-03, these results have to be tempered.

Local administration of extended-release formulation of BPV and MLX (HTX-011-10) was more efficient than extended-release formulation of BPV (HTX-002-01) between 24-48 hrs with the same tendency up to 72 hrs. Regarding HTX-009-03, analgesia scores were the lowest observed throughout all the time-period demonstrating that MLX alone was not sufficient to provide a satisfying analgesic effect. Overall, MLX seems to prolong the analgesic efficacy of BPV after 24 hrs. Based on these results and scores obtained up to 24 hrs. post-incision, it appears that release of BPV and MLX or time residency at the local site of administration were different.

The applicant has highlighted that systemic administration of MLX does not enhance analgesic efficacy of locally administrated BPV alone in the extended-release formulation. Indeed, superiority of HTX-011-56 over HTX-002-13 could be accepted until 24 hrs and after 48hrs even though high variability has been observed.

PK profile of HTX-011-56 has been investigated throughout PK studies of various extended-release formulations in rat and dog species. Although the PK development program is consequent many uncertainties remain and lack of some studies have not been justified by the applicant.

The CHMP did not require any new animal studies since it appears from the dossier that no correlation can be drawn between animal PK vs Human PK. In addition, it can also be said that no correlation can be made between *in vitro* release and *in vivo* PK.

Uncertainties remain due to the lack of the knowledge of local concentration in BPV and MLX and the effect observed. It is acknowledged that an extended release is observed for the two substances, however the regimen of delivery from the polymer seems different based on systemic levels. Indeed, BPV is massively and rapidly released from the polymeric support whereas MLX's release is slower and with a lower intensity. Therefore, based on concentrations, efficacy observed during pharmacological studies is difficult to be properly understood.

In study 33-79, the applicant did conclude that no sex differences were observed for BPV, however high variation in Tmax value measured for BPV (25 mg/kg) is observed between male (6 hrs) and female (30 min) rats. The same tendency is observed with the highest dose in BPV (50 mg/kg). Moreover, it appears that Tmax and T1/2 for BPV and MLX in rats are different whatever the sex chosen whereas similarity was observed for both substances in pigs (study 33-87). In addition, from Study Report 33-79 mean concentration-time profiles are different in terms of curve shape between BPV and MLX. Therefore, the applicant was expected to discuss the difference observed in curve shape and possible relationship with extended release. The applicant underlines that inter-animal variability and sample assay variability can result in differences in mean Tmax and attributed to the plateau in BPV observed until 12 hrs post dose. This information did not appear in PK profile presented for BPV in study 33-79. A similar answer was given for MLX based on limited number of sampling time points in the terminal phase and this is acknowledged. MLX t1/2 value presented in the dog PK study (study 33-36) has shown high variability with an important SD, therefore mean-concentration time profiles for MLX (study 33-36) are of weak interest since it is based on pool values with a high SD. Therefore, information generated during PK studies are not very supportive. The applicant considered that "curve shapes" of bupivacaine and meloxicam in rats in study 33-79 appear different because the clearance is very different for these compounds. Although the applicant relied on IVR study to ascertain that BPV and MLXD release are equivalent and differences observed in the curve shapes in rats study are related to different kinetic of clearance. Nevertheless, in vivo results in animals have shown difference in terms of PK profile therefore IVR cannot be considered as supportive to describe similarity of release between the two substances and no in vitro/in vivo correlation can be drawn.

As observed in study 33-79, it has been observed during study 33-36 that PK profiles for BPV and MLX are different in dog species (study 33-36) with curve shapes "similar" in rats and dogs, however no sex difference was observed. Based on observed Tmax and T1/2 higher for MLX vs BPV, the applicant was expected to discuss why these results are not observed in pig species and which animal species is the most relevant to Human in terms of PK properties. The applicant identifies the rat species as being the most relevant to humans in terms of PK properties. This is substantiated from the data obtained from the applicants' own studies as well as literature reports. The applicant has discussed further the differences on Tmax and T1/2 that are higher for meloxicam vs bupivacaine in different species. Differences in the meloxicam PK curves between pigs and rats and dogs are due to the faster clearance of meloxicam in pigs ([Pig (mature; ~220 kg) CL= 0.72 mL/min/kg vs Dog (~12 kg) CL= 0.15 mL/min/kg]; Busch 1998, Pairis-Garcia 2015). The issue was considered as resolved.

The applicant did not conduct any study regarding distribution of HTX-011-56 based on structure similarity with the polymer used in SUSTOL. Nevertheless, those two polymers are not 100% identical and less is known regarding the impact of bupivacaine and meloxicam in distribution. Moreover, data provided by the applicant revealed that the distribution study seems to have been performed with the unloaded polymer i.e. without the active substance. However, based on the presented results, it is expected that the highest mean concentration of HTX-011-56 would be observed at the injection site. In addition, presence of the two active substances may have an impact on the overall physico-chemical parameters of the polymer and therefore distribution may be modified. Thus, the applicant had to justify the lack of distribution studies with HTX-011-56. The applicant has submitted a justification for the lack of distribution studies with HTX-011-56 in line with the provisions of article 10b of Directive 2001/83/EC.

Zynrelef is a medicinal product containing active substances used in the composition of other authorised medicinal products but not hitherto used in combination for therapeutic purposes. Taking the above into consideration, Directive 2001/83/EC codifies that results of new pre-clinical tests or new clinical trials relating to that combination shall be provided in a stand-alone new marketing authorization application (article 8(3)), however, it shall not be necessary to provide scientific references relating to each individual active substance. The applicant also referred to study 24-21 that evaluated the distribution and excretion of the TEG-POE polymer used in HTX 011 56 and discusses that polymer remains at the administration site until it is hydrolysed. While study Report 24-21, indicates that the administration site has the highest concentration of polymer at 24 hours postdose, before significant hydrolysis occurs, which is the same with HTX-011-56. The applicant concludes that although the active ingredients have an impact on their release rate from the formulation, they do not impact the physico-chemical properties of the TEG-POE polymer. Taking all the arguments put forward on the lack of distribution studies with HTX-011-56, the applicant's justification is upheld.

Study 33-78 has demonstrated that Lidocaine co-administration with HTX-011-56 did not result in any significant modification of the individual PK parameters of BPV and MLX.

In study 33-47, based on the PK results the applicant has demonstrated that presence of MLX into the polymer does not modify PK properties of BPV since similarity PK profile was observed for BPV in the two extended-release formulations HTX-011-56 and HTX-002-13 (BPV only).

In study 33-69, based on the PK results the applicant has highlighted that presence of BPV seems to interact with PK profile of MLX. It appears that in the extended-release formulation containing only MLX i.e. HTX-009-05, MLX is absorbed faster as shown by earlier Tmax and a higher Cmax. This aspect is in opposition to what was observed previously. Thus, the applicant was expected to discuss why BPV presence modifies PK profile of MLX whereas MLX has no effect on BPV PK properties. The applicant has acknowledged that MLX is absorbed faster from HTX-009-05 (MLX only) than HTX-011-56 (BPV and MLX co-formulation). Although PK profiles seemed different, AUCs observed in MLX (for the same loading) were on the same range. The applicant did conclude that no metabolic-drug interaction was observed and this position is endorsed.

Regarding the release from the polymeric support, the applicant has agreed that differences observed are related to the formulation. Applicant's demonstration relies on the hydrolysis of the polymer moiety that requires protons to be engaged. Since BPV base was integrated into the polymer, the applicant has indicated that protonation of BPV would result in protecting the polymeric moiety from degradation (throughout hydrolysis process) and therefore MLX's release, wherein no BPV is added into the polymer, would be shorter. Based on IVR data of MLX from HTX-009-05 and HTX-011-56, the applicant has concluded that extended-release of MLX in HTX-009-05 occurred over 48 hrs. vs 72 hrs. in presence of BPV. Therefore, it was concluded that the difference in MLX PK profile was due to the difference of the formulation and not any biological interactions between BPV and MLX. This explanation could not be fully endorsed. Indeed, it is acknowledged that extended-released is observed for the two compounds, however differences were observed during in vitro studies and PK in vivo studies (study 33-79, study 33-36…). From the IVR of BPV and MLX in HTX-011-10, it appears that competition in terms of release from the polymeric support is observed in favour of BPV. The kinetic of release of BPV is faster in the first 24 hrs. for BPV in comparison with MLX. This phenomenon is supported by mean BPV concentration observed in vivo PK studies wherein a massive release is observed quickly. These aspects demonstrate that MLX's release from the polymeric support is not governed by BPV protonation, preventing hydrolysis of the polymer. Otherwise, MLX's release would be faster than BPV after the deposit. Therefore, the release from the polymeric is based on a diffusion-related process in favour of BPV. Indeed, in vivo animal PK studies have underlined that extended-release was observed for both substances, nevertheless this extended-release is sustained with low BPV concentrations whereas higher MLX's concentrations are observed. Thus based on these animals it can only be concluded that a massive burst

release in BPV is observed rapidly and remaining concentrations are released slowly over the time-period. In the other hand, MLX's PK profile in animals is more common to a classical extended release. Efficacy observed during pharmacology studies is finally difficult to interpret based on animal PK profile since it appears that BPV seems to be rapidly found in plasma (high concentrations) and it is not known which is the lowest local concentration sufficient in BPV in order to a pharmacological effect occurs. Shift in MLX's release is in favour of sustaining the effect of BPV, however there is not a full understanding of the mechanism based on pharmacology and PK studies. Thus, PK data cannot explain what is observed and no translation to Human can be made in terms of PK.

Overall, the applicant believes that study 24-21 provides sufficient information on the distribution of the TEG-POE moiety in HTX-011-56. Nevertheless, as previously mentioned behaviour of the fully loaded polymer (with the two active substances) may differ from APF18A polymer.

No nonclinical pharmacodynamics drug interaction studies were conducted with HTX-011-56. PD drug interactions of BPV and MLX alone are known and therefore information in drug PD interactions is available from clinical experience.

Anaesthetics are known to have the potential to enhance the CNS toxicity (respiratory depression) of concomitantly applied opioids (e.g. Becker DE: Adverse drug reactions in dental practice. Anaesth Prog 2014, 61:26-34). Therefore, the applicant provided a thorough discussion concerning the CNS safety of bupivacaine/opioid combinations on basis of published non-clinical data to provide a justification for the absence of own non-clinical interaction studies on this issue.

The impurity levels in the batches of drug product used in the nonclinical safety (and clinical) studies were generally very low or not detected. Impurities levels have been treated in accordance with current guidelines and the presented limits are acceptable.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical dossier is sufficient to support Marketing Authorisation Application for Zynrelef.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 4: Overview of HTX-011 clinical studies

Study No.	Study Design and Population	Treatments (N)a
Phase 1		
02 (The Netherlands)	Open-label, saline placebo-controlled, single-ascending dose, PK, safety, and PD	• HTX-011-19: 100 mg/3 mg (N=11), 200 mg/6 mg (N=5), or 400 mg/12 mg (N=11) via

Section 2.7.2.2.1.1.1	study of 2 earlier HTX-011 formulations in healthy adult volunteers	subcutaneous injection • HTX-011-49: 100 mg/3 mg (N=5) or 200 mg/6 mg (N=5) via subcutaneous injection • Saline placebo via subcutaneous injection (N=9)
102 (US) Section 2.7.2.2.1.1.2	Phase 1, PK, safety, tolerability in healthy Volunteers	• HTX-011-56 400 mg/12 mg via subcutaneous injection (N=10)
Phase 2a		
202 (US) Section 2.7.2.2.1.1.3	Randomized, blinded, placebo- and active-controlled safety, efficacy, and PK study in subjects who underwent herniorrhaphy	• HTX-011-56 200 mg/6 mg via instillation (N=16) or injection (N=16) • HTX-011-56 300 mg/9 mg via instillation (N=16) • HTX-011-56 400 mg/12 mg via instillation (N=21), injection (N=14), or combination of injection and instillation (N=48) • HTX-002 200 mg via instillation (N=12) or injection (N=9) • HTX-002 400 mg via instillation (N=15) or injection (N=15) • HTX-009 12 mg via combination of injection and instillation (N=12) • HTX-011-19 200 mg/6 mg via injection (N=19) or instillation (N=16) • HTX-011-19 400 mg/12 mg via injection (N=17), instillation (N=20), or combination of injection and instillation (N=17) • HTX-011-49 200 mg/6 mg via injection (N=20) • HTX-011-49 400 mg/12 mg via injection (N=19) • Saline placebo via injection or combination of injection and instillation (N=103) • Bupivacaine HCl 0.25% 75 mg via injection (N=32)
203 (US) Section 2.7.2.2.1.1.4	Randomized, blinded, placebo- and activen controlled safety, efficacy, and PK study in subjects who underwent mini- or complete abdominoplasty	<u>Mini-abdominoplasty</u> • HTX-011-56 200 mg/6 mg via injection (N=10) • HTX-011-56 400 mg/12 mg via injection (N=11) or combination of injection and instillation (N=17) • HTX-011-56 600 mg/18 mg via injection (N=10) • HTX-002 400 mg via combination of injection and instillation (N=17) • HTX-011-49 200 mg/6 mg via injection (N=20)

		• Saline placebo via injection (N=63) Complete abdominoplasty • HTX-011-56 300 mg/9 mg via combination of injection and instillation (N=35) • HTX-011-56 400 mg/12 mg via instillation (N=17) or combination of injection and instillation (N=24) • Saline placebo via injection (N=32) • Bupivacaine HCl 0.25% 100 mg via injection (N=17)
208 (US) Section 2.7.2.2.1.1.5	Randomized, blinded, placebo- and active-controlled safety, efficacy, and PK study in subjects who underwent bunionectomy	• HTX-011-56 30 mg/0.9 mg via injection using Mayo block (N=18) • HTX-011-56 60 mg/1.8 mg via instillation (N=17), injection (N=17), or injection using Mayo block (N=18) • HTX-011-56 120 mg/3.6 mg via instillation (N=37), injection (N=19), or injection using Mayo block (N=18) • HTX-011-56 200 mg/6 mg via injection (N=15) or injection using Mayo block (N=15) • HTX-002 60 mg via injection (N=12) or injection using Mayo block (N=11) • HTX-002 120 mg via injection (N=15) or injection using Mayo block (N=15) • HTX-002 200 mg via injection (N=6) or injection using Mayo block (N=5) • HTX-009 3.6 mg via injection (N=15) or injection using a Mayo block (N=14)HTX-011-49 200 mg/6 mg via injection (N=16) or injection using Mayo block (N=16) • Saline placebo via injection or injection using a Mayo block (N=104) • Bupivacaine HCl 0.5% 50 mg via injection or injection using a Mayo block (N=25)
Phase 2b		
209 (US) Module 2, Section 2.7.3.2.2.1.3	Phase 2b, randomized, double blind, placebo- and active controlled efficacy, safety, and PK study in subjects who underwent total knee arthroplasty	Cohort 1: • HTX-011-56 200 mg/6 mg via periarticular instillation (N=20) • HTX-011-56 200 mg/6 mg via a combination of periarticular injection and instillation (N=20) • Saline placebo via periarticular injection (N=11) • Bupivacaine HCl 0.25% 125 mg via periarticular injection (N=10) Cohort 2: • HTX-011-56 400 mg/12 mg via

		periarticular instillation and ropivacaine 50 mg via periarticular injection (N=56) • HTX-011-56 400 mg/12 mg via periarticular instillation (N=53) • Saline placebo via periarticular injection (N=53) • Bupivacaine HCl 0.25% 125 mg via periarticular injection (N=55)
211 (US) Module 2, Section 2.7.3.2.2.2.1	Phase 2b, randomized, double blind, placebo- and active controlled efficacy, safety, and PK study in subjects who underwent augmentation mammoplasty	• HTX-011-56 60 mg/1.8 mg via bilateral ultrasound-guided lateral and medial pectoral nerve block (N=12) • HTX-011-56 120 mg/3.6 mg via bilateral ultrasound-guided lateral and medial pectoral nerve block (N=26) • HTX-011-56 240 mg/7.2 mg via bilateral ultrasound-guided lateral and medial pectoral nerve block (N=24) • HTX-011-56 400 mg/12 mg via bilateral ultrasound-guided lateral and medial pectoral nerve block (N=47) • HTX-011-56 400 mg/12 mg via instillation (N=49) • Saline placebo via bilateral ultrasound-guided lateral and medial pectoral nerve block (N=41) • Bupivacaine HCl 0.25% 50 mg via bilateral ultrasound-guided lateral and medial pectoral nerve block (N=41)
Phase 3		
301 (US) Module 2, Section 2.7.3.2.2.1.1	Phase 3, randomized, double-blind, placebo- and active-controlled efficacy, safety, and PK study in subjects who underwent bunionectomy	• HTX-011-56 60 mg/1.8 mg via instillation (N=157) • Saline placebo via instillation (N=101) • Bupivacaine HCl 0.5% 50 mg via injection (N=154)
302 (US and Europe) Module 2, Section 2.7.3.2.2.1.2	Phase 3, randomized, double-blind, placebo- and active-controlled efficacy, safety, and PK study in subjects who underwent herniorrhaphy	• HTX-011-56 300 mg/9 mg via instillation (N=161) • Saline placebo via instillation (N=82) • Bupivacaine HCl 0.25% 75 mg via injection (N=173)

2.4.2. Pharmacokinetics

Bupivacaine and meloxicam are approved in several regions and have a long history of clinical use. Bupivacaine is a local anesthetic and meloxicam a nonsteroidal anti-inflammatory drug (NSAID). Inclusion of low-dose meloxicam in HTX-011 reduces local inflammation caused by surgery and normalizes the local pH, which is supposed to enhance bupivacaine penetration into nerves, thereby potentiating bupivacaine analgesic effect.

HTX-011-056 is a solution that is formulated in a proprietary Tri(ethylene glycol)-based poly(orthoester) polymer (TEG-POE polymer), termed Biochronomer®. For the TEG-POE polymer, which have been

previously used for another product SUSTOL (granisetron) for which the FDA have granted a MA, two studies using human biomaterial were provided in this dossier (Study 34-14 and Study 33-04) which have evaluated the water-soluble end products from the hydrolysis of TEG-POE in human plasma and have characterized TEG-POE metabolites using cryopreserved human hepatocytes.

The clinical pharmacology investigations has been performed in healthy volunteers (HV) first then in patients and consisted of two Phase I in HV, three Phase 2a, two Phase 2b and two Phase III studies, as shown in Table 6. In addition, preliminary results from an ongoing Phase 4 study are provided to support bridging of the proposed HTX-011 formulation vs the bupivacaine reference medicine.

Full PK profiling has been performed in all the studies. Five PK modeling analyses were conducted to support the clinical pharmacology of HTX-011 as shown below.

Table 5: PK modeling studies

Study Report Number	Report Name	Modeling Objectives
34-16	Population PK and Exposure-Response Modeling Report	• Evaluate variability and identify covariates that may impact bupivacaine and meloxicam PK. • Determine model-based estimates of the distribution of bupivacaine C_{max} for each surgical procedure. • Develop an ER model describing the relationship between bupivacaine exposure and pain intensity scores. • Evaluate the effect of subject covariates on the ER model for bupivacaine.
34-12	Renal Impairment Population PK Modeling Report	• Simulate the PK of TEG, TEG acid, PEMPA, and PE in subjects with renal impairment
33-82	Hepatic Impairment Modeling Report	• Simulate the PK of bupivacaine in subjects with hepatic impairment
34-27	Integrated ECG Safety Report for Studies 209, 211, 302, and 302	• Determine the effects of bupivacaine and meloxicam systemic exposure on ECG intervals including QTcF

Abbreviations: C_{max}, maximum observed concentration; ECG, electrocardiogram; ER, exposure-response; PE, pentaerythritol; PEMPA, pentaerythritol monopropionate; PK, pharmacokinetic(s); QTcF, QT interval corrected for heart rate using Fridericia's formula; TEG, triethylene glycol; TEG acid, triethylene glycol monocarboxylic acid.

Absorption

HTX-011 and bupivacaine HCl have been investigated in various soft tissue (herniorrhaphy, augmentation mammoplasty) and bony (bunionectomy, TKA) surgical models covering a range of sizes and vascularity. In addition to several surgical models, different HTX-011 formulation containing bupivacaine and meloxicam (HTX-011-019, HTX-011-049 and HTX-011-056) or bupivacaine alone (HTX-002) or meloxicam alone (HTX-009), and different route of administration (SC injection, instillation or combination) were investigated. Table 6 provides a summary of bupivacaine and meloxicam PK parameters following administration of HTX-011-056 via instillation. Figure 7 and Figure 8 present concentration time-profiles of bupivacaine and meloxicam respectively.

Table 6: Summary of PK parameters for bupivacaine and meloxicam following a single dose of HTX-011-056 via instillation

Active Ingredient	Parameter	Bunionectomy: 60 mg/1.8 mg ZYNRELEF (N = 17)	Herniorrhaphy: 300 mg/9 mg ZYNRELEF (N = 16)	Total Knee Arthroplasty: 400 mg/12 mg ZYNRELEF (N = 109)
Bupivacaine	C_{max} (ng/mL)	53.6 (32.6)	271 (147)	672 (411)
	t_{max} (h)	3.00 (1.55-24.08)	18.22 (3.10-30.28)	20.87 (3.98-59.95)
	$AUC_{(0-t)}$ (h×ng/mL)	1,650 (1,130)	14,900 (8,470)	31,300 (20,900)
	$AUC_{(inf)}$ (h×ng/mL)	1,680 (1,190)	15,300 (8,780)	33,300 (22,300)
Meloxicam	C_{max} (ng/mL)	25.6 (13.8)	225 (96.3)	270 (139)
	t_{max} (h)	18.02 (8.13-60)	53.72 (24.2-96.02)	36.18 (8.13-73.98)
	$AUC_{(0-t)}$ (h×ng/mL)	1,600 (915)	18,600 (7,860)	17,500 (10,500)
	$AUC_{(inf)}$ (h×ng/mL)	1,660 (1,050)	15,500 (NC[a])	18,700 (9,920)

Figure 7: Mean PK profiles for bupivacaine following instillation of HTX-011-056

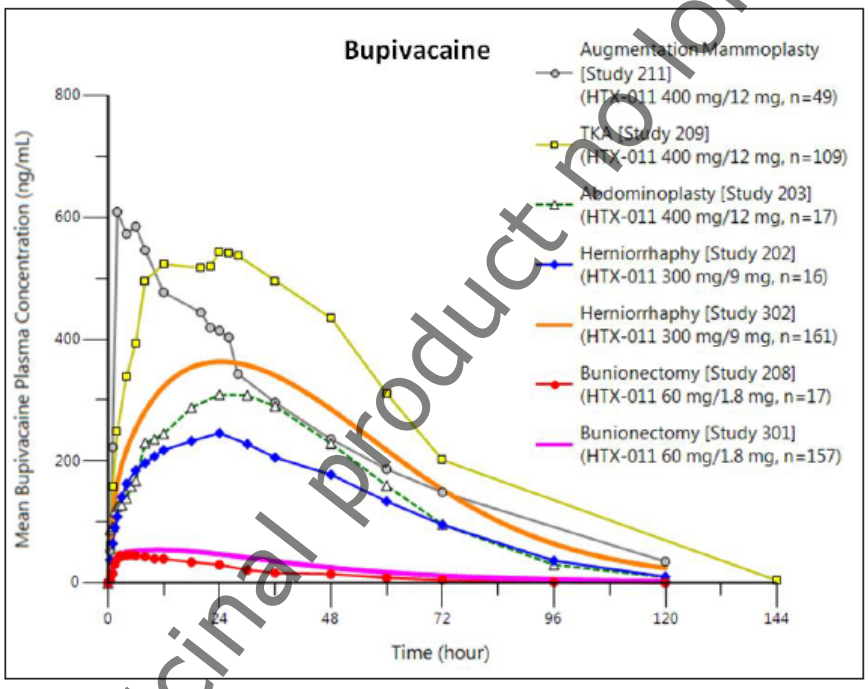
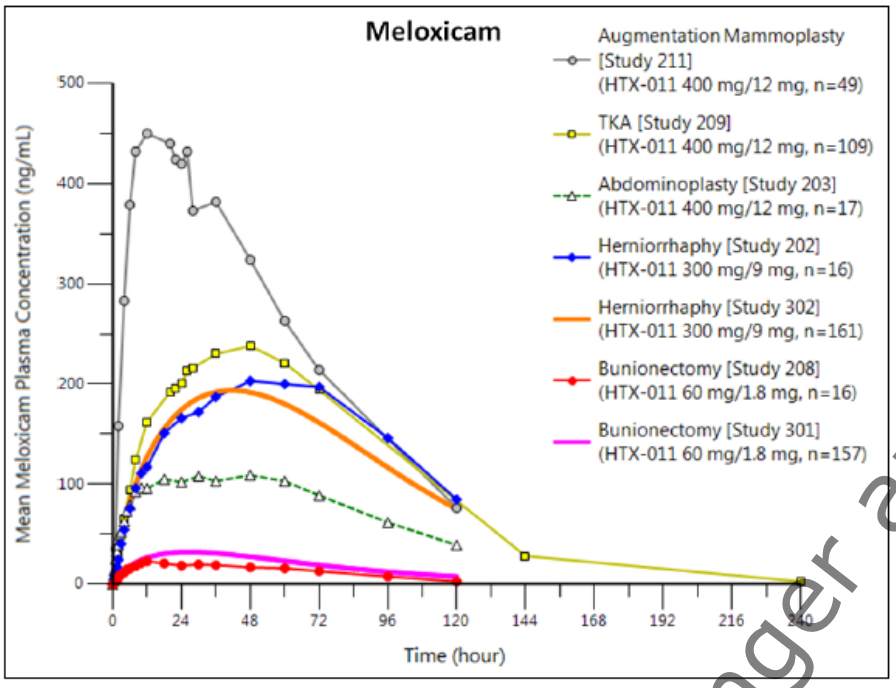


Figure 8: Mean PK profiles for meloxicam following instillation of HTX-011-056



From the extended release formulation at 24h median % cumulative bupivacaine released ranged from 36.2 % to 45.3% (Bunionectomy to TKA) whereas for meloxicam at 24h, median % cumulative bupivacaine released ranged from 22.3 % to 30.1% (Bunionectomy to TKA).

Distribution

The applicant relied upon the prescribing information from MARCAINE and MOBIC where estimated Vd were 73 L and 11 L respectively for bupivacaine and meloxicam after IV administration in healthy volunteers.

Elimination

- **Excretion**

Following instillation of HTX-011-056, the mean terminal half-life of bupivacaine, and across surgery type, ranged from 9.11 h to 14 h (herniorrhaphy to bunionectomy). For mammoplasty terminal half-life ranged from 14.4 h to 21.8h.

Following instillation of HTX-011-056, the mean terminal half-life of meloxicam, and across surgery type, ranged from 17.8 h to 28.8 h (herniorrhaphy to bunionectomy).

The excretion of water-soluble end products was evaluated in Study 102 following a single administration of HTX-011 400 mg/12 mg via subcutaneous injections. Approximately 83.6% and 92.0% of total PE (PE plus PEMPA) and total TEG (TEG plus TEG acid), respectively, were excreted in urine, indicating that urinary excretion is the major elimination pathway for these TEG-POE-derived water-soluble end products and metabolites.

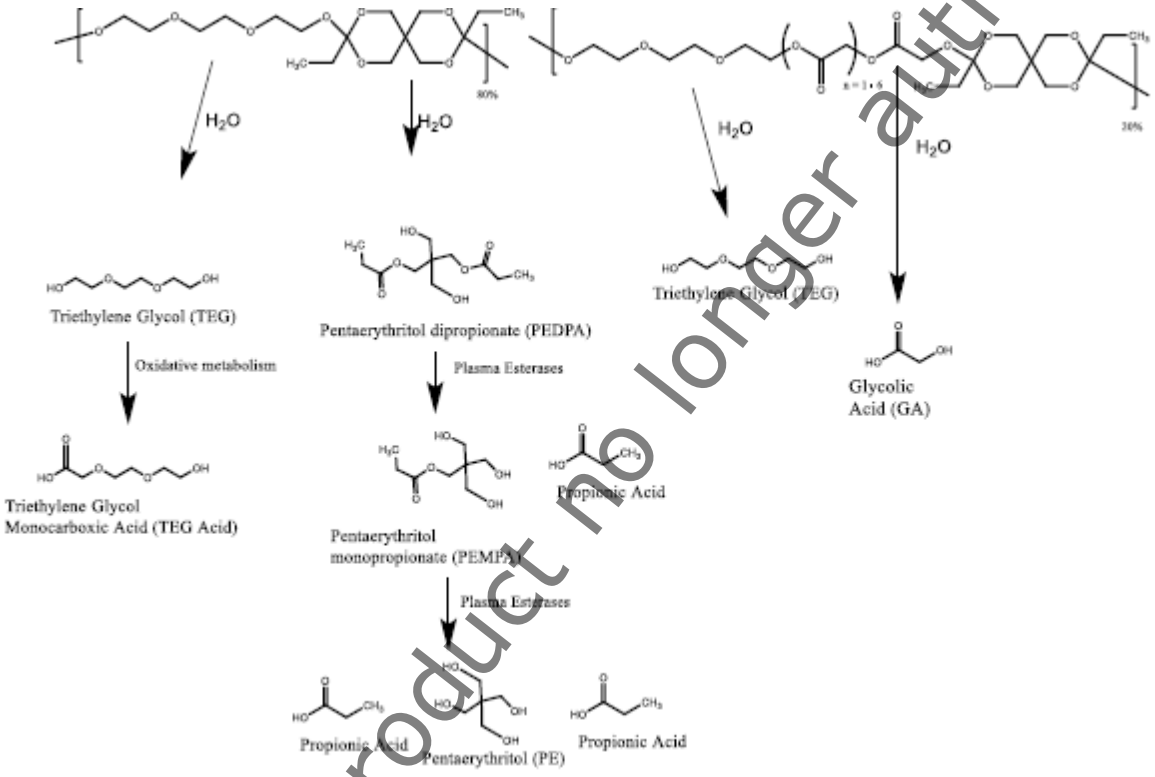
- **Metabolism**

For bupivacaine and meloxicam, the applicant rely upon the prescribing information for approved MARCAINE and bupivacaine solution for injection (MARCAINE USIP 2015, Bupivacaine Injection SmPC 2017); and MOBIC and meloxicam solution for injection (MOBIC Tablets USPI 2016, Meloxicam Injection

SmPC 2017). After bupivacaine and meloxicam have been released form HTX-011 and are absorbed systematically, the metabolism is expected to be the same as for bupivacaine and meloxicam oral formulations.

For TEG-POE polymer, the metabolism has been investigated in 2 human biomaterials studies (Studies 34-14 and 33-04) and 1 Phase 1 clinical study. Studies 34-14 and 33-04 were performed during the MAA of another product, FDA-approved SUSTOL which is formulated with vehicle, APF18A, which is composed of 80% TEG-POE polymer (SUSTOL USPI 2017). TEG-POE undergoes hydrolysis to TEG, GA, and pentaerythritol dipropionate that is then enzymatically hydrolyzed to PEMPA and PA.

Figure 9: Hydrolysis pathway of TEG-POE (AP135) Polymer



Dose proportionality

According to the applicant, Bupivacaine mean Cmax for HTX-011 in the Phase 2 and Phase 3 studies increased linearly for doses ranging from 30 mg/0.9 mg to 400 mg/12 mg across multiple surgical procedures (R2=0.8581), regardless of vascularity of the surgical site or method of administration. The same trend was observed for AUC (R2=0.9627). Similarly to bupivacaine, meloxicam mean Cmax and AUC increased linearly for doses ranging from 30 mg/0.9 mg to 400 mg/12 mg, regardless of the surgical site or method of administration.

However, dose linearity have not been formally demonstrated with the claimed administration technique and across the surgery types. This is particularly highlighted in Table 10, where dose proportionality is unlikely.

Time dependency

Time-dependency has not been formally investigated since the drug product would be administered once.

Intra- and inter-individual variability

Results from the PPK analysis show that IIV for bupivacaine was particularly high 70.7% and 116% respectively for CL/F and Vc/F. For meloxicam IIV was also particularly high 69.8 % and 84.6 % for CL/F and Vc/F respectively.

Pharmacokinetics in target population

The developed PPK models appear to adequately characterize the PK of bupivacaine and meloxicam, however a critical issue with regard to the estimate value of the apparent distribution volume for both compounds suggest a refinement of the PPK model. Nevertheless such refinement remain not needed as unreliable Vds do not have an influence on the absorption phase, which is the process of interest.

Special Populations

Impaired renal function

Bupivacaine-Meloxicam

No formal study was performed to investigate impaired renal function on PK of bupivacaine and meloxicam. Based on the results from the PPK of bupivacaine and meloxicam, creatinine was not tested as a covariate since according to the applicant no graphical trend was observed (ETA-PK vs creatinine). In the studied population mean observed creatinine was 73.9 µM (range: 38.9-147 µM). No eGFR was estimated. The applicant rely upon the prescribing information for approved products. After bupivacaine and meloxicam have been released form HTX-011 and are absorbed systematically, the effects of renal impairment are expected to be the same as for bupivacaine and meloxicam oral formulations.

TEG-POE polymer

The effects of renal impairment on the PK of water-soluble end products of TEG-POE (PEMPA, PE, TEG and TEG-acid) from HTX-011 was investigated using PK modelling with PK data from Study 102. Study 102 was a Phase I, single-center, single dose in healthy volunteers. Two PPK models were developed, one for PE and PEMPA and one for TEG and TEG acid using PK plasma and urine samples.

PEMPA and PE PPK model

Simulation of HTX-011 polymer hydrolysis products (PEMPA, PE, TEG and TEG acid) were performed in 1000 adult subjects per renal impairment groups using the developed final PPK. Results of this analysis show that, there are minimal differences in PEMPA Cmax and AUCinf between the renal impairment groups. In female the Cmax is 20% and AUCinf 10% greater than male. For PE,as renal function become worse, PE Cmax and AUCinf increase from 20% to 175% (mild to severe vs normal). And For TEG and TEG acid impaired renal function have a minor effect of PK exposure metrics of both.

Impaired hepatic function

No formal study was performed to investigate impaired hepatic function on PK of bupivacaine and meloxicam. Based on the results from the PPK of bupivacaine and meloxicam, Albumin, ALP, ALT, AST, bilirubin were not tested as covariates since according to the applicant no graphical trend was observed. (ETA-PK vs hepatic function covariates). In the studied population mean observed albumin was 42.7 g/L (29.5-52.1 g/L), mean ALP was 73.1 U/L (14-167 U/L), mean ALT was 21.4 U/L (5-125 U/L), mean AST was 21.1 U/L (8-77 U/L), mean bilirubin was 8.75 µM (1.03-39.3µM) and were similar across the different surgical procedure.

The applicant rely upon the prescribing information approved for approved products. After bupivacaine and meloxicam have been released form HTX-011 and are absorbed systematically, the effects of hepatic impairment are expected to be the same as for bupivacaine and meloxicam oral formulations.

However, since bupivacaine is known to be highly metabolized by liver enzymes and can cause toxicities in patients with liver impairment due to a reduction in clearance, the effects of hepatic impairment on the PK of bupivacaine from HTX-011 have been investigated using PK modelling based on PK data from Study 202. Results of this analysis indicated that hepatic impairment have a modest impact on the Cmax of bupivacaine, ranging from 4.8% to 12.5% for injection and instillation respectively.

Weight

Weight was found to have a significant effect on Vp/F of bupivacaine and on Vc/F of meloxicam.

Gender, race, age

Based on the results from the PPK models for bupivacaine and meloxicam, gender, race or age have no effect on the PK of both bupivacaine and meloxicam, since no graphical trend was observed.

Interactions

No DDI studies were conducted with HTX-011. At the proposed recommended highest dose of HTX-011, mean plasma Cmax of bupivacaine and meloxicam from HTX-011 have been shown to be lower than those of approved bupivacaine and meloxicam products, respectively, within the proposed recommended doses.

The likelihood of a DDI between bupivacaine and meloxicam in HTX-011 is low based on an evaluation of in vitro data of the disposition of each drug reported in published literature as well as clinical data from HTX-011 studies showing no clinically meaningful changes in PK exposure between each active ingredient administered alone (ie, HTX-002 or HTX-009) or together in HTX-011.

Exposure relevant for safety evaluation

Model-based simulation of bupivacaine Cmax

Bupivacaine concentration profiles were simulated based on the final bupivacaine PK model (excluding the residual error. Simulations were performed for the inguinal herniorrhaphy (300 mg HTX-011), bunionectomy (60 mg HTX-011), augmentation mammoplasty (400 mg HTX-011) and total knee arthroplasty (400 mg HTX-011) surgeries over a range of weights (median and 2.5th and 97.5th percentiles: 76, 54 and 118 kg, respectively). The provided simulation for Cmax bupivacaine clearly show that the rate of occurrence of potential CNS effect is low at the 400 mg dose of bupivacaine used for mammoplasty or TKA (respectively 2.2% for overweight and 0.6% for low weight subjects).

Evaluation of the effect of HTX-011-056 on QTcF interval

ECG-plasma concentration relation from two Phase 2b (Study 209 and Study 211) and two Phase 3 (Study 301 and Study 302) clinical trials of HTX-011 was investigated. For each study HTX-011 plasma concentrations were investigated on four endpoints, QTcF, HR, PR and QRS. No global analysis with all the available PK/PD were performed.

Overall the exposure-response modelling appears to demonstrate a shortening of the QTcF interval for both bupivacaine and meloxicam with no discussion by the applicant.

Exposure-efficacy (Pharmacokinetic/ Pharmacodynamic)

Exposure-Efficacy

An exposure-response (ER) model was developed with the objective to describe bupivacaine effect on pain score. The ER include PK/PD data from three surgery type bunionectomy (Study 208 and Study 301), herniorrhaphy (Study 202 and Study 302) and TKA (Study 209). PK/PD data from mammoplasty (Study 211) were excluded since no appropriate placebo comparator was available and PK/PD data from abdominoplasty (Study 203) were also discarded (during the PPK model development).

Given that the analgesic effects of local anesthetics occur locally at the site of administration, systemic bupivacaine plasma concentrations are a surrogate for the local concentration and were used to calculate bupivacaine release rate from HTX-011. Bupivacaine release rate, which was calculated as the combined rate of zero-order and first-order bupivacaine absorption in the population PK model, represents the rate at which bupivacaine is released from the HTX-011 formulation and enters the surgical site to be available for analgesia. In order to characterize the effect of HTX-011 on pain score, separate models were developed for the time-dependent decrease in pain scores in subjects receiving saline placebo (ie, placebo model) and the additional drug-dependent decrease in pain scores in subjects receiving HTX-011 ie, ER model). An indirect response model with bupivacaine absorption or release (mg/hr) driving a sigmoid maximum effect of drug exposure (Emax) model of pain relief describes the decreases in pain score. In addition, an exponential decay function (known as the "narcotic" effect) describes the increase in pain immediately following surgery as the effects of anesthesia and perioperative analgesia (eg. from lidocaine or fentanyl) diminished.

First a time-dependent model for pain scores for subject receiving placebo was developed first, then results from this analysis were used to estimate the additional effects of HTX-011 in a separate ER model. Overall for both PD model, PD parameter were estimated with a good precision, however the associated IIV was particularly high from 46.5% to 18583%. In addition, many of the PD parameter were highly correlated questioning the reliability of the developed PK/PD model.

Finally, the main result from this analysis is the link between the release rate of bupivacaine (expressed in mg/h) from HTX-011 to the pain score. Therefore, we could not rule out that HTX-002 (bupivacaine alone) produces the same result because it is supposed to be released at the same rate as HTX-011.

2.4.3. Pharmacodynamics

Mechanism of action

HTX-011-56 is a novel, extended-release, fixed dose combination product that contains bupivacaine, an amide-type local anaesthetic, and low-dose meloxicam, a nonsteroidal anti-inflammatory drug. The rationale for this combination therapy is that generally analgesic efficacy of local anaesthetics, including bupivacaine, is affected by inflammation which creates a local acidic environment (Hargreaves, 2002; Ueno, 2008). This in turn favours the ionized form of bupivacaine thus limiting its penetration into the nerve membrane. This may be the reason for the reduced analgesic efficacy of bupivacaine alone in inflamed tissues. The addition of an NSAID, i.e. meloxicam, to bupivacaine may reduce the local inflammation and normalize the pH at the surgical site. This leads to an increase in the un-ionized lipid-soluble form of bupivacaine able to penetrate the nerve membrane and results in enhanced analgesia. Meloxicam demonstrated the optimal profile of potency (to allow a practical dose for incorporation in the matrix) and other physicochemical properties, such as solubility, for use in combination with bupivacaine formulated with the TEG-POE polymer.

Therefore, in case of Zynrelef, meloxicam is not used for its analgesic properties but is believed to reduce local inflammation and normalize local pH, resulting in a significantly greater analgesic effect at lower bupivacaine doses, and therefore a longer duration of bupivacaine's effect (enhanced penetration into the nerves). These arguments are endorsed even though those did not exclude analgesic effect of

meloxicam. The brand-new polymer developed by the applicant would then constitute also a support to the increase duration of bupivacaine's efficacy allowing controlled extended release of the active substances during 72 hours.

The indication claimed by the applicant for the association of bupivacaine and low dose meloxicam is not different from the one associated to bupivacaine alone (relief of post-operative pain) and the distinction is related to the duration of action: Zynrelef has been developed in order to obtain a longer-lasting postoperative analgesic. This could be considered as the new therapeutic claim.

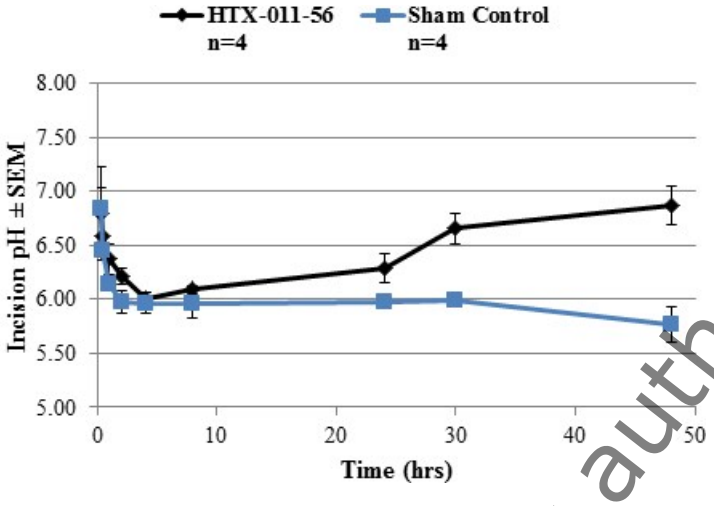
For fixed combination medicinal product, Applicants are required to justify the pharmacological and medical rationale for the particular combination of active substances and for the intended therapeutic indication. Clinical development should correspond to the intended claim.

The applicant underlined key elements of the application. Local acidic environment following surgery is believed to contribute to the limited duration of local anesthetic effect even with continued exposure and that increasing the pH favors the nonprotonated form of bupivacaine, permitting more bupivacaine to enter the nerve and increasing analgesia. Therefore, local administration of nonsteroidal anti-inflammatory drugs (NSAIDs) would be expected to limit the local inflammatory response and inhibit the production of tissue prostaglandins, thereby reducing the local inflammatory-mediated tissue pH drop and peripheral sensitization. This is endorsed.

According to the applicant, Zynrelef meets the criteria of a fixed combination product in that it offers greater (in magnitude and duration) overall effect in postoperative analgesia compared to monotherapy with bupivacaine HCl, the current standard of care. This was overall shown in phase 3 studies in bunionectomy with osteotomy (301) and open inguinal herniorrhaphy (302). However, the bupivacaine doses (standard of care) were inferior to the doses of bupivacaine contained in the FDC Zynrelef and used for comparison. As a consequence, it was not possible to formally assess the contribution of meloxicam in the proposed FDC Zynrelef in those phase 3 studies.

Nonclinical data in domestic piglet are suggested by the applicant to confirm that a surgical incision in results in rapid local tissue acidosis, which is reversed with meloxicam in HTX-011.

Figure 10: Change in Incision Site Intra-Dermal pH Over Time in the Domestic Piglet Postoperative Pain Model



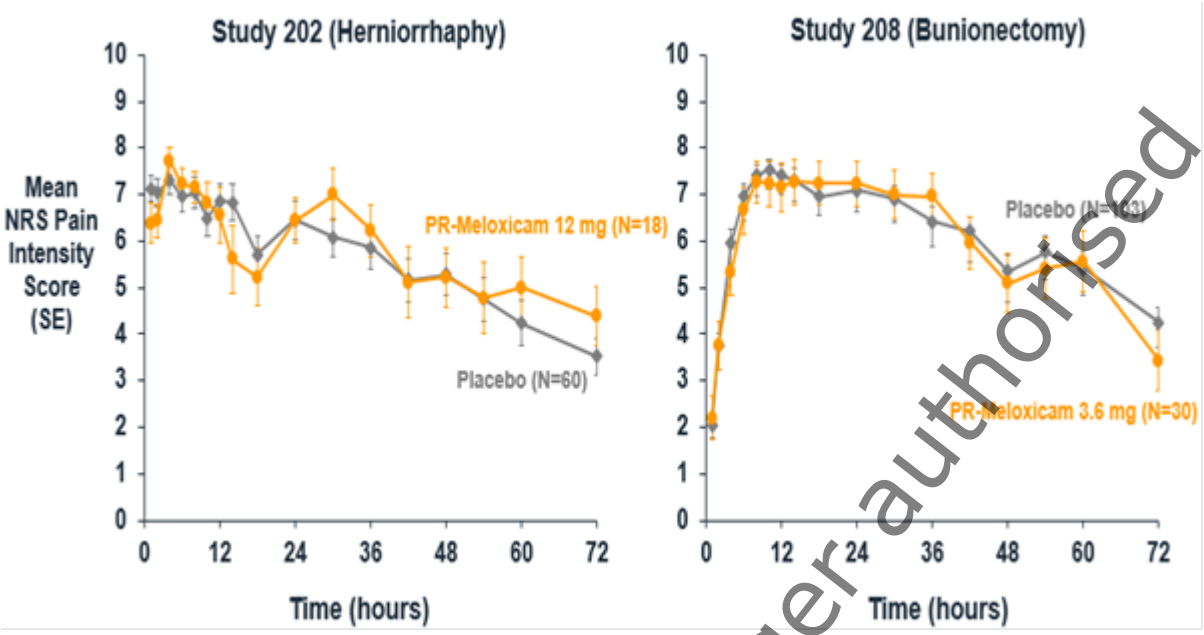
Regarding the claim of synergy between meloxicam and bupivacaine, meloxicam alone having no to minimal analgesic activity, the applicant proposes a rational for the FDC based on section 4.3. "Initial combination treatment" of the "Guideline on clinical development of fixed combination medicinal products" (EMA/CHMP/158268/2017) […] "*The design of clinical efficacy/safety studies to support a fixed combination medicinal product application for initial treatment will depend on its rationale, specifically to achieve superior efficacy or improved safety compared to use of the single active substances*" […] Option C "*One (or more) active substance has no individual efficacy in the targeted indication*" : "*If one (or more) of the active substances has no efficacy in the targeted indication by itself and compelling mechanistic data (e.g. using biomarkers) would suggest a synergistic effect, mechanistic data (e.g. in vitro data), preclinical and human PD data may be sufficient to support a claim of improved efficacy of the fixed combination medicinal product instead of (stepwise) up-titration or addition of those active substances in a clinical efficacy/safety study. Still, improved efficacy over (an) individual active substance(s) that have established efficacy in the targeted indication needs to be shown as usual. The design of the pivotal clinical studies should be according to specific clinical guidance, where placebo or standard of care – instead of these individual active substances - may be acceptable as comparators. A direct comparison against individual active substances with established efficacy in the targeted indication would still be expected*".

Clinical evidence of the role of meloxicam in the FDC came from two phase 2 studies. Study 202 and study 208 were phase 2, randomized, pilot studies to investigate the safety, efficacy, pharmacokinetics and bioavailability of HTX-011, HTX-002, or HTX-009 administered via injection and/or topical application following unilateral open inguinal herniorrhaphy and bunionectomy with osteotomy, respectively. Several formulations, administrations technics, and doses of the FDC were tested. In addition, formulations of the polymer with respectively bupivacaine (HTX-002) or meloxicam (HTX-009) alone were also tested.

The analgesic synergy of the combined active substances was suggested by the following:

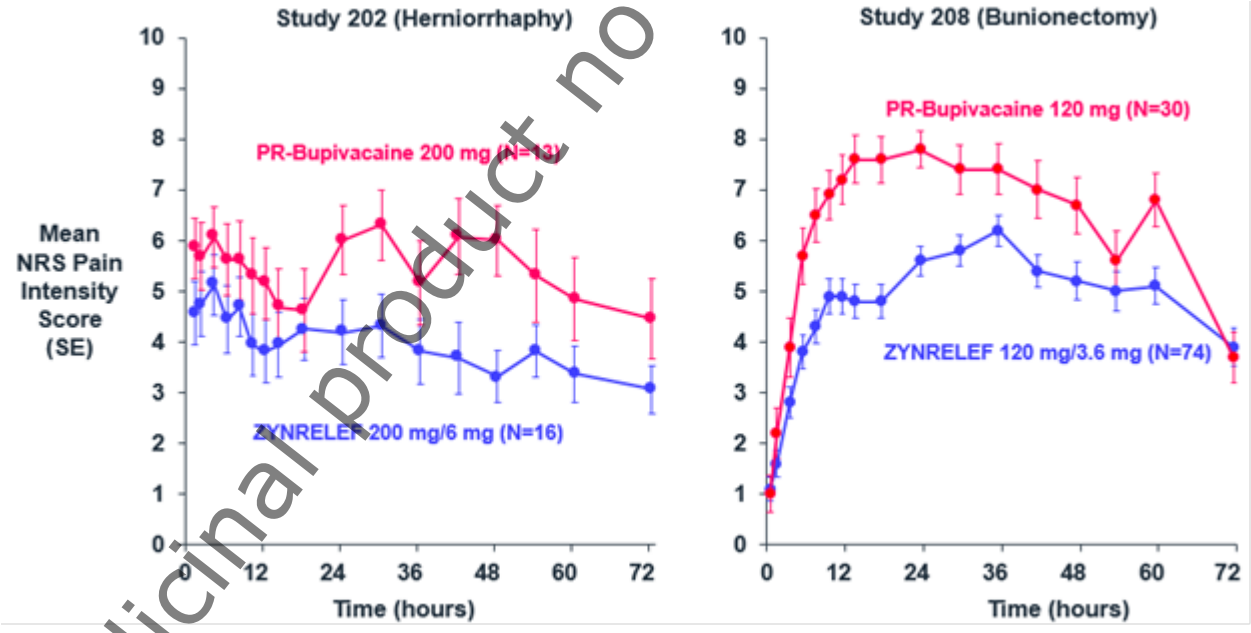
1. Prolonged-release meloxicam (HTX-009) had negligible effect on postoperative pain

Figure 11



2. The efficacy of Zynrelef was superior to that of prolonged-release bupivacaine (HTX 002) at the same bupivacaine doses.

Figure 12

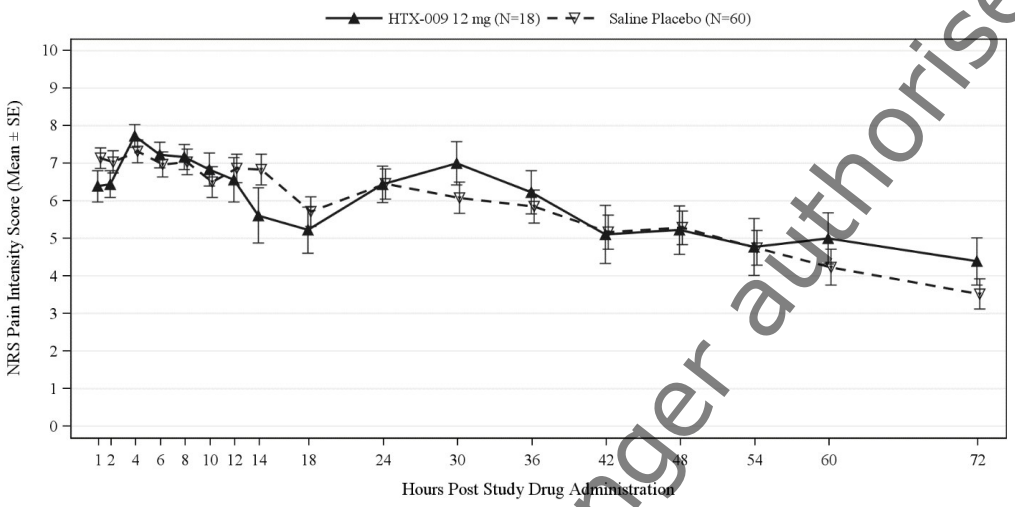


These studies presented several limitations that led to question the exact role of meloxicam in the FDC. Indeed, an assessment of the contribution of each of the substances of the FDC in the indication based on a comparison on small effective at a non-optimal dose and including not just only the claimed administration method (instillation) raises uncertainties. It is endorsed that study 202 and 208 suggest efficacy of the FDC in postoperative pain. However, these studies were not designed to formally demonstrate synergy between bupivacaine and meloxicam.

The applicant acknowledged that neither Study 202 nor Study 208 formally demonstrated synergy between meloxicam and bupivacaine or negligible inherent analgesic effect of meloxicam. However, the applicant stated that "the replicated evidence of the superior efficacy of HTX-011 compared with

prolonged-release bupivacaine, demonstrated using the same endpoint and analysis method as in the Phase 3 studies, supports the potentiating effect of meloxicam on the activity of bupivacaine, justifying the role of meloxicam in the FDC". This was considered acceptable.

Figure 13



Furthermore, the choice of meloxicam (active ingredient) rather than another substance (excipient) has been adequately justified by the applicant after an initial concern raised. Similarly, the rationale for the selection of meloxicam over another NSAID been adequately justified by the applicant

Primary and Secondary pharmacology

Proof-of-Concept Study in Healthy Volunteers

Study 02

Study 02 was a phase 1, first-in-human, proof-of-concept study used to demonstrate dose-dependent, antinociceptive effects of earlier formulations, HTX-011-19 and HTX-011-49, with extended duration in a human pain model.

Study Design and Objectives:

Open-label, saline placebo-controlled, single-ascending dose study investigating the PK, safety, tolerability, and PD of 2 earlier clinical formulations (HTX-011-19 and HTX-011-49) in healthy adult volunteers.

The study was conducted in 3 parts.

Table 7

Study Part	Objectives	Treatments
Part I	Primary: assess PK of bupivacaine and meloxicam after single ascending subcutaneous doses of HTX-011-19. Secondary: • assess safety and local tolerability after single ascending subcutaneous doses of HTX-011-19. • assess PD after single ascending subcutaneous doses of HTX-011-19.	Subjects (N=18) received single, ascending doses of HTX-011-19 (100 mg/3 mg, 200 mg/6 mg, or 400 mg/12 mg) or saline placebo via subcutaneous, divided injections in the upper part of the right leg.
Part II	Primary: assess and compare the analgesic and anesthetic effects of three different, single, subcutaneous doses of HTX-011-19. Secondary: • assess PK, safety and local tolerability of three different single, subcutaneous doses of HTX-011-19.	Subjects (N=16) were randomized to either HTX-011-19 (100 mg/3 mg or 400 mg/12 mg) or saline placebo. The Minimal Erythema Dose (MED) of UVB light was determined for each subject during the screening period. Twenty hours prior to dosing, each subject was exposed to 3 times the MED of UVB light on the upper part the right leg, which was followed by study drug administration via subcutaneous, divided injections in the same area.
Part III	Primary: assess PK of bupivacaine and meloxicam after single ascending subcutaneous doses of HTX-011-49. Secondary: • assess safety and local tolerability after single ascending subcutaneous doses of HTX-011-49. • assess PD after single ascending subcutaneous doses of HTX-011-49.	Subjects (N=12) were randomized to receive either HTX-011-49 (100 mg/3 mg or 200 mg/6 mg) or saline placebo via subcutaneous, divided injections in the upper part of the right leg.

Criteria:

The mechanical detection threshold (MDT), mechanical pain threshold (MPT), cold pain threshold (Part II only), and heat pain threshold (Part II only) were assessed for PD effects of HTX-011-19 or HTX 011-49 at pre-dose on Day 1 and at specified time-points through Day 7 on the area where study drug was administered. For all study parts, blood samples were collected from each subject at prespecified timepoints through Day 7 for the determination of bupivacaine and meloxicam PK in plasma.

Safety and tolerability parameters assessed throughout the study included adverse events (AEs), local tolerability, vital signs, ECG recordings, and clinical safety laboratory findings. A follow-up examination was conducted on Day 12, and all treatment-emergent AEs (TEAEs) were followed to resolution or Day 28 after dosing.

Subject Population:

A total of 46 subjects were randomized and received study drug:

27 received HTX-011-19 (100 mg/3 mg (N=11), 200 mg/6 mg (N=5), or 400 mg/12 mg (N=11)) via subcutaneous injection, 10 received HTX-011-49 (100 mg/3 mg (N=5) or 200 mg/6 mg (N=5)) via subcutaneous injection and 9 received saline placebo. The majority of subjects were male (56.5%) and White (97.8%) with a 100 mg/3 mg (N=5) or 200 mg/6 mg (N=5) via subcutaneous injection mean (SD) age of 27.9 (9.3) years.

Forty-five subjects completed study assessments through the Follow-up Visit.

Pharmacodynamic Results:

In Part I, the mechanical thresholds for detection and pain increased with dose, with maximum MDT values obtained at 6 hours (100 mg/3 mg dose level), 12 hours (200 mg/6 mg dose level), and 24 hours (400 mg/12 mg dose level).

In Part II, there were trends for dose-dependent effects on mechanical thresholds for detection and pain on skin irradiated with ultraviolet B light. The maximum effect on MDT at HTX-011-19 400 mg/12 mg dosing was approximately 2.5 times higher than at 100 mg/3 mg dosing. The duration of maximum effect was also longer at 400 mg/12 mg dosing (24 hours post-dose) compared with 100 mg/3 mg (4 hours post-dose).

In Part III, there was faster onset of the effects on the mechanical thresholds for detection and pain observed with HTX-011-49 as compared with HTX-011-19 in Parts I and II. The duration of effects, however, was also shorter lasting for HTX-011-49 as compared with HTX-011-19.

In study 02, dose-dependent effects on MDT and MPT were observed with HTX-011-19 and HTX-011-49. PD data are indicative of a dose-dependent, antinociceptive effect with extended duration in a human pain model.

The formulations of HTX-011-19 and HTX-011-49 do not correspond to the finished product (Zynrelef/HTX-011) and were administrated by subcutaneous injection whereas Zynrelef/HTX-011 is intended to be administrated by instillation.

Finally, it is difficult to consider this study as a "proof of concept" study because exact role of meloxicam and polymer has not been assessed.

2.4.4. Discussion on clinical pharmacology

The clinical pharmacology data of HTX-011 are supported by 7 clinical studies in adult patients (Study 202, 203, 208, 209, 211, 301 and 302) and one clinical study in healthy volunteers (Study 102). The clinical development program covers 5 different type of surgery (bunionectomy, herniorrhaphy, total knew arthroplasty, abdominoplasty and mammoplasty) from which several administration techniques were tested (injection, instillation, combination of injection and instillation).

Rich sampling was performed in all clinical studies, except those associated to the pivotal studies (Study 301 and 302) where sparse PK sampling was performed. Therefore, summary of the PK exposure parameters provided in the dossier came from results from the developed PPK analysis for bupivacaine and meloxicam.

Generally, based on the validation reports, the used bioanalytical methods developed for the quantification of bupivacaine, meloxicam in human plasma and the end-products of the TEG-POE polymer in both plasma and urine, comply with acceptance criteria. Analytical validation reports were provided with satisfactory results.

The PK of both bupivacaine and meloxicam is considered well known, therefore the applicant relies upon the prescribing information for approved products for distribution, DDI and elimination.

In general, following instillation of HTX-011:

- bupivacaine Tmax ranged from 3h (bunionectomy) to 18.22-20.87 h (herniorrhaphy-TKA) whereas for meloxicam Tmax ranged 18h (bunionectomy) to 36.2-53.7h (TKA-herniorrhaphy) suggesting that meloxicam released from the polymer is delayed. This is confirmed by the release rate of each compound (36.2 to 45.3% at 24h for bupivacaine and 22.3% to 30% for meloxicam).
- Apparent volume of distribution of bupivacaine Vz/F estimated by NCA, and across surgery type ranged from 218 L to 1430 L (herniorrhaphy to bunionectomy) suggesting strong tissue distribution. This finding was not confirmed by PPK analysis where an apparent central and peripheral distribution volume were estimated at 12.2 L and 29.3 L. Similar discrepancies were observed for meloxicam and both are attributable to flip flop kinetics.
  However, a concern remain with regards to the discrepancy between the estimated value of apparent distribution volume of both compounds from the PPK analysis and the value reported in the SmPC suggesting an update of the developed PPK models.
- Mean terminal half-life for bupivacaine ranged from 9.11 h to 14 h (herniorrhaphy to bunionectomy) whereas for meloxicam the mean terminal half-life and across surgery type, ranged from 17.8 h to 28.8 h (herniorrhaphy to bunionectomy).

Dose proportionality was claimed for both bupivacaine and meloxicam from 30 mg /0.9 mg to 400 mg / 12 mg whatever the administration technique and the surgery type. However the claimed administration technique is instillation and the claimed indication is not endorsed since several surgery type are investigated where "*extrapolation of safety and efficacy from local application at one surgical site to another surgical site is difficult due to different anatomical conditions such as magnitude of the surgical area and vascularization*".

Consequently, it should be noted that the results presented by the applicant cover all surgical procedure tested in clinical trials (bunionectomy, herniorrhaphy, TKA, abdominosplasty, mammoplasty) and all administration techniques (injection, instillation and combination) used in these trials whereas it was expected, at this stage, a demonstration of dose linearity with the claimed administration technique (instillation) for a specific surgery type. Based on the individual reports and Applicants methodology "Dose proportionality was concluded if the 90% CI for the slope was completely contained within the pre-specified acceptance range for Cmax and AUC values [0.8-1.25]", dose proportionality is not demonstrated whatever the surgery type with the instillation technique. The issue will not be pursued since dose proportionality is not claimed by the applicant in the SmPC, and to note based on the Table 2 provided in the SmPC for both bupivacaine and meloxicam, it remains obvious that dose proportionality is not demonstrated.

A separate PPK model was developed for bupivacaine and meloxicam. The PPK model for bupivacaine was developed sequentially with first PK data from Studies 202 and 203, then after discarding PK data from Study 203, with PK data from Studies 202 and 208. Then predictive performance of the build base PK model was evaluated using NPDE with PK data from Studies 209 and 211, and finally PK data from Studies 301 and 302 were added. Overall, the applicant PK model building process remain unclear. Particularly the evaluation of predictive performance of the base PK model using only graphical evaluation with NPDE without computing the associated statistics of interest (mean, variance, skewness, kurtosis…) instead of using metrics to evaluate bias and imprecision would have been useful for the purpose.

Overall, the PPK model for bupivacaine fits for purpose when all PK data were pooled. ETA-shrinkage for PK parameters associated to the absorption process were particularly high. This suggest that available PK data from certain surgery type does not provide sufficient information to derive reliable individual PK parameters. Finally, results from the developed PPK model were used in a simulation exercise for a safety

purpose and for the description of the release of bupivacaine and meloxicam; and as input to the PK/PD analysis for bupivacaine.

A PK/PD model was developed from which results should be interpreted with cautions, since to note individual PK parameters used as input to estimate the release rate have a high shrinkage, and the final PD parameters are associated to a huge IIV from 46.5% to 18583% with PD parameters highly correlated. The main result is the link between bupivacaine released from the polymer (expressed in mg/h) associated to the decrease of the pain score. This suggest that we could not rule out that HTX-002 (bupivacaine alone) produces the same result because it is supposed to be released at the same rate than HTX-011.

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics is considered adequately characterized in terms of absorption, distribution and elimination. However a issue was raised with regards to the estimate value of the apparent distribution volume for both compounds and that suggest a refinement of the PPK model. Nevertheless, such refinement will not be needed as unreliable Vds do not have an influence on the absorption process.

Demonstration of synergy between meloxicam and bupivacaine has been demonstrated sufficiently, despite a number of limitations of the clinical development.

2.5. Clinical efficacy

Table 8: Overview of HTX-011 Studies Supporting the Proposed Indication

Study No. (Region)	Study Design	Surgical Procedure	Treatment Groups (ITT/mITT Population)	Analysis	Type of Model	Anatomic Space
Pivotal Studies						
Phase 3						
301 (US)	Randomized, double-blind, placebo- and active-controlled efficacy, safety, and PK study	Bunionectomy	• HTX-011 60 mg/1.8 mg (N=157) • Saline placebo (N=100) • Bupivacaine HCl 0.5% 50 mg (N=155)	• Efficacy • Exposure-response	Bony	Small
302 (US and Europe)	Randomized, double-blind, placebo- and active-controlled efficacy, safety, and PK study	Herniorrhaphy	• HTX-011 300 mg/9 mg (N=164) • Saline placebo (N=82) • Bupivacaine HCl 0.25% 75 mg (N=172)	• Efficacy • Exposure-response	Soft tissue	Medium
Phase 2b						

Study No. (Region)	Study Design	Surgical Procedure	Treatment Groups (ITT/mITT Population)	Analysis	Type of Model	Anatomic Space
209[a] Cohort 2 (US)	Randomized, double-blind, placebo- and active-controlled efficacy, safety, and PK study	Total knee arthroplasty	• HTX-011 400 mg/12 mg + ropivacaine 0.5% 50 mg (N=56) • HTX-011 400 mg/12 mg (N=58) • Saline placebo (N=53) • Bupivacaine HCl 0.25% 125 mg (N=55)	• Efficacy • Exposure-response	Bony	Large
Supportive Studies						
Phase 2b						
209[a] Cohort 1 (US)	Randomized, double-blind, placebo- and active-controlled efficacy, safety, and PK study	Total knee arthroplasty	• HTX-011 200 mg/6 mg (N=20) • Saline placebo (N=11) • Bupivacaine HCl 0.25% 125 mg (N=10)	• Efficacy • Exposure-response	Bony	Large
211[b] (US)	Randomized, double-blind, placebo- and active-controlled efficacy, safety, and PK study	Augmentation mammoplasty	• HTX-011 400 mg/12 mg (N=50) • Saline placebo (N=41) • Bupivacaine HCl 0.25% 50 mg (N=41)	• Efficacy	Soft tissue	Large
Phase 2a						
208[c] (US)	Phase 2a, randomized, blinded, placebo- and active-controlled safety, efficacy, and PK study	Bunionectomy	• HTX-011 60 mg/1.8 mg* (N=17) • HTX-011 120 mg/3.6 mg (N=37) • Saline placebo (N=103) • Bupivacaine HCl 0.5% 50 mg (N=25)	• Efficacy • Exposure-response	Bony	Small

Study No. (Region)	Study Design	Surgical Procedure	Treatment Groups (ITT/mITT Population)	Analysis	Type of Model	Anatomic Space
202[c] (US)	Phase 2a, randomized, blinded, placebo- and active-controlled safety, efficacy, and PK study	Herniorrhaphy	• HTX-011 200 mg/6 mg (N=16) • HTX-011 300 mg/9 mg* (N=16) • HTX-011 400 mg/12 mg (N=21) • Saline placebo (N=83) • Bupivacaine HCl 0.25% 75 mg (N=32)	• Efficacy • Exposure-response	Soft tissue	Medium

Abbreviations: ITT, Intent-to-Treat; mITT, modified Intent-to-Treat; PK, pharmacokinetics; US, United States.
Notes: HTX-011 (also referred to as HTX-011-56) is the intended commercial formulation and was the only formulation evaluated in the Phase 3 and Phase 2b studies. The ITT Population included all subjects who were randomized and received study drug (Studies 301, 302, and 209). The mITT Population included all subjects in the ITT Population who had at least 1 postdose scheduled pain intensity score (Studies 211, 208, and 202).
* Doses selected for Phase 3.
[a] Study 209 included 2 sequential cohorts. Cohort 1 was a dose-finding cohort. Cohort 2 was adequate and well-controlled.
[b] Study 211 was a Phase 2b nerve block study that included 1 treatment group of HTX-011 administered via instillation. Only HTX-011 administered via instillation (intended commercial route of administration) and the 2 controls (saline placebo and bupivacaine HCl) administered via nerve block and pooled across cohorts are presented.
[c] Only the intended commercial formulation of HTX-011 (also referred to as HTX-011-56) and doses of HTX-011 administered via the intended commercial route of administration (instillation) are presented (pooled across cohorts).
Bupivacaine dose is mentioned first then the meloxicam dose in HTX-011

2.5.1. Dose response study(ies)

The applicant did not conduct any dose response studies. The clinical development was focused on the different types of surgeries (bunionectomy and herniorrhaphy in particular). Phase II studies were design to lead the applicant, for each type of surgery on the selection of:

- The optimal formulation;
- The optimal administration technique;
- The optimal doses of the fixed dose combination.

Bunionectomy: Study 208

"A Phase 2, Randomized, Controlled, Multicenter, Evaluation of the Efficacy and Safety of Locally Administered HTX-011, HTX-002, or HTX-009 for Postoperative Analgesia Following Bunionectomy".

This study was designed to evaluate the safety, efficacy, and PK of 2 HTX-011 formulations (HTX-011-49 and HTX-011-56) administered as a single dose via local administration into the surgical site via different techniques in adult subjects undergoing unilateral simple bunionectomy.

Saline placebo and bupivacaine HCl 0.5% without epinephrine were employed as controls. Two HTX-011-56 comparators, HTX-002 (bupivacaine only) and HTX-009 (meloxicam only), were also included to evaluate the contribution of the APIs to the effects of HTX-011-56.

The primary efficacy endpoint was the summed pain intensity score (SPI) over the first 24 hours (SPI0-24).

A total of 430 subjects were randomized and received study drug. 423 (98.4%) completed the study. 17 subjects were randomized in HTX-011 60 mg / 1.8 mg administered by instillation with a Luer-Lock applicator group (the selected dose and administration technique for the phase 3 study).

HTX-011-49 formulation was discontinued during the course of this study due to preliminary PK data.

The minimum effective dose that produced statistically significant reductions in SPI0-24 compared with bupivacaine HCl was HTX-011-56 60 mg/1.8 mg (primary endpoint). All administration techniques were effective at reducing pain. Systemic exposures (bupivacaine and meloxicam) were higher with injection techniques compared to instillation techniques. There appeared to be a dose-dependent increase in the incidence of overall TEAEs.

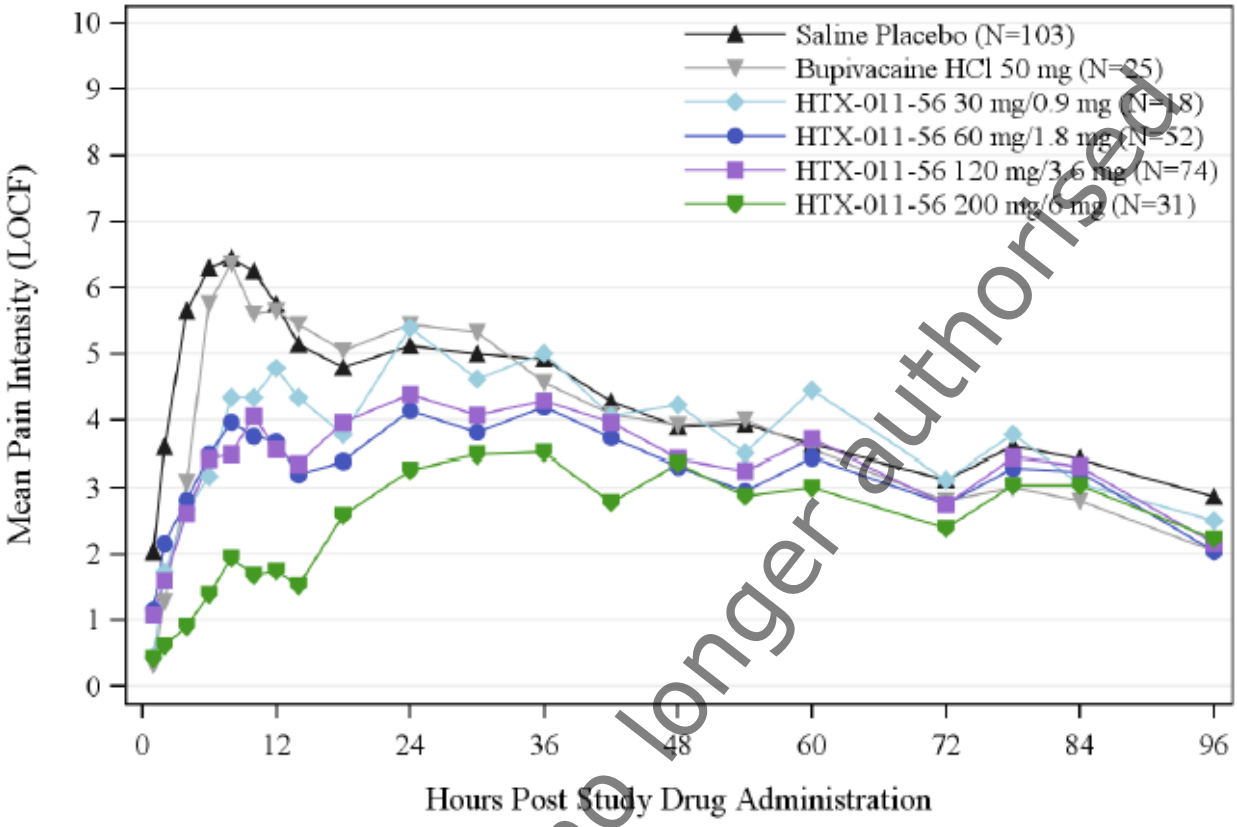
Thus, the optimal HTX-011 formulation, dose, and administration technique to reduce postoperative pain with a favourable safety profile in subjects undergoing bunionectomy was determined by the applicant to be HTX-011-56 60 mg/1.8 mg via instillation using a Luer-lock applicator. This dose was selected for the phase 3 study in bunionectomy.

Table 9: Primary Endpoint: Mean SPI0-24 by HTX-011-56 Dose Group vs. Saline Placebo and Bupivacaine HCl (LOCF, mITT Population)

HTX-011-56 Dose Group	N	Mean (SD)	Control	N	Mean (SD)	P-value
30 mg/0.9 mg	18	96.83 (50.151)	Saline placebo[a]	31	136.39 (38.670)	0.0033
			Bupivacaine HCl 50 mg[a]	5	94.60 (48.557)	0.9302
60 mg/1.8 mg	52	83.38 (46.226)	Saline placebo	103	126.46 (47.785)	<0.0001
			Bupivacaine HCl 50 mg	25	118.16 (50.634)	0.0037
120 mg/3.6 mg	74	85.70 (40.716)	Saline placebo	103	126.46 (47.785)	<0.0001
			Bupivacaine HCl 50 mg	25	118.16 (50.634)	0.0017
200 mg/6 mg	31	49.23 (40.781)	Saline placebo	103	126.46 (47.785)	<0.0001
			Bupivacaine HCl 50 mg	25	118.16 (50.634)	<0.0001

Abbreviations: LOCF, last observation carried forward; mITT, modified Intent-to-Treat; SPI, summed pain intensity.
Notes: Statistics reflect results of an analysis of variance (ANOVA). Administration techniques were pooled for the HTX-011-56 60 mg/1.8 mg to 200 mg/6 mg dose groups and the corresponding controls used as comparators.
[a] Administered via injection using a Mayo block.
Source: Table 14.2.1.1.

Figure 14: Mean Pain Intensity Scores over time by HTX-011-56 Dose Group vs. Saline Placebo and Bupivacaine HCl (LOCF, mITT Population)



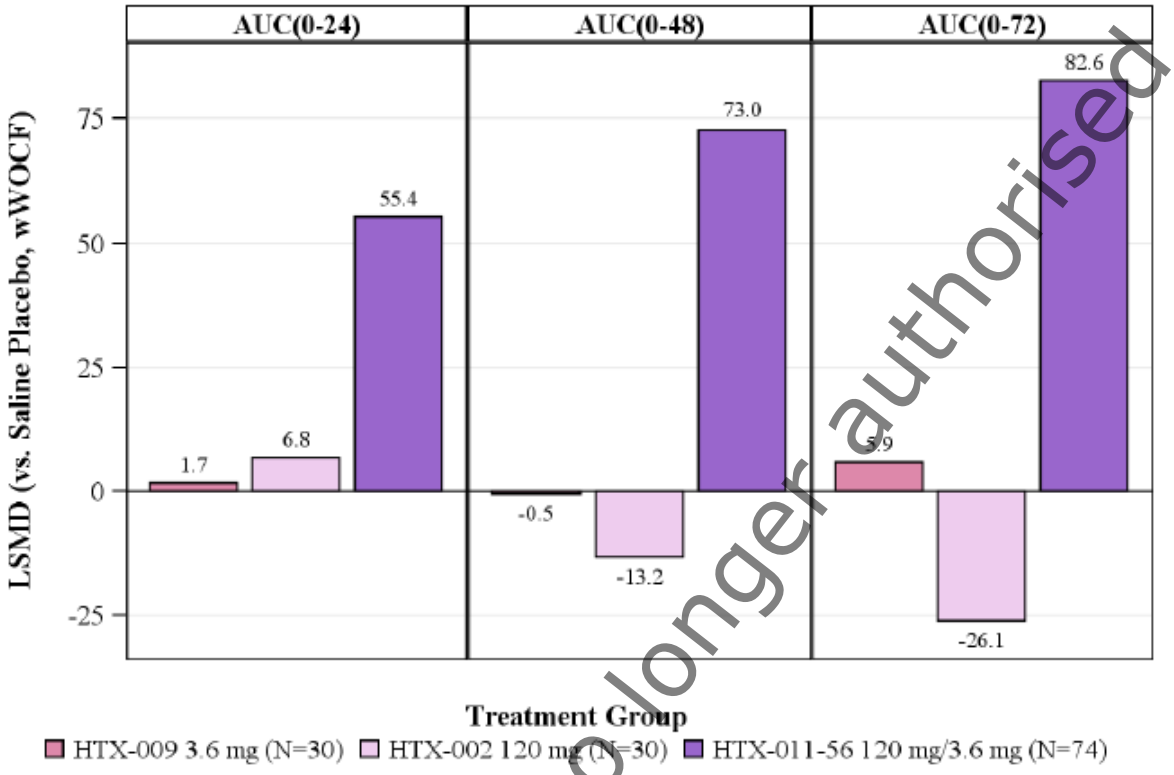
Contribution of HTX-011 components to the reduction in mean AUC of pain intensity scores was assessed using least squares mean difference with HTX-011-56 120 mg/3.6 mg, HTX-002 120 mg and HTX-009 3.6 mg compared to placebo. HTX-011-56 120 mg/3.6 mg reduced pain more effectively than equivalent doses of either comparator: HTX-002 120 mg or HTX-009 3.6 mg. Furthermore, the reduction in pain intensity was more than the sum of the 2 comparators. In addition, an assessment of reduction in pain intensity was performed comparing HTX-011-56 against extended-release bupivacaine (HTX-002) and immediate-release bupivacaine (bupivacaine HCl).

Table 10: Mean AUC of Pain intensity Score for HTX-011-56 vs. HTX-002 (wWOCF, mITT Population)

	HTX-011-56 60 mg/ 1.8 mg (N=52)	HTX-002 60 mg (N=23)	HTX-011-56 120 mg/ 3.6 mg (N=74)	HTX-002 120 mg (N=30)	HTX-011-56 200 mg/ 6 mg (N=30)	HTX-002 200 mg (N=11)	Bupivacaine HCl 150 mg (N=25)
AUC_{0-24}							
Mean (SD)	101.60 (52.904)	132.42 (40.916)	99.22 (50.476)	147.84 (51.103)	54.82 (47.577)	108.04 (61.815)	143.02 (53.864)
p-value vs. HTX-002	0.0154		<0.0001		0.0054		
AUC_{0-48}							
Mean (SD)	224.59 (100.579)	281.78 (86.691)	236.28 (97.872)	322.48 (101.045)	159.70 (94.066)	253.08 (113.446)	306.54 (114.674)
p-value vs. HTX-002	0.0208		0.0001		0.0106		
AUC_{0-72}							
Mean (SD)	332.35 (153.566)	411.42 (124.925)	351.46 (152.177)	460.17 (144.577)	246.36 (133.411)	400.29 (183.641)	430.11 (183.942)
p-value vs. HTX-002	0.0333		0.0011		0.0050		

Abbreviations: AUC, area under the curve; mITT, modified Intent-to-Treat; wWOCF, windowed worst observation carried forward.
Source: Table 14.2.5.3.

Figure 15: Contribution of HTX-011 Components to the Reduction in Mean AUC of Pain Intensity Scores: HTX-011-56 120 mg/3.6 mg vs. HTX-002 120 mg and HTX-009 3.6 mg (wWOCF, mITT Population)



Abbreviations: AUC, area under the curve; LSMD, least squares mean difference; mITT, modified Intent-to-Treat; wWOCF; windowed worst observation carried forward.
Note: HTX-002 and HTX-009 have similar compositions to HTX-011-56 except HTX-002 contains only bupivacaine as the active pharmaceutical ingredient (API) and HTX-009 contains only meloxicam as the API.
Source: Table 14.2.5.3.

Table 11: Mean AUC of pain intensity scores for placebo, bupivacaine HCl, HTX-002, HTX-009 and HTX-011-56 (wWOCF, mITT Population)

Mean AUC of pain intensity scores	Placebo (N=103) Injection with or without a Mayo block	Bupivacaine HCl (50 mg) (N=25) Injection with or without a Mayo block	HTX-002 (bupivacaine 120 mg) (N=30) Injection with or without a Mayo block	HTX-009 (meloxicam 3.6 mg) (N=30) Injection with or without a Mayo block	HTX-011-56 (bupivacaine 120 mg / meloxicam 3.6 mg) (N=74) Injection with or without a Mayo block + instillation with or without a Luer-lock applicator

AUC 0-24 (SD)	154.66 (49.168)	143.02 (53.864)	147.84 (51.103)	152.94 (52.829)	99.22 (50.476)
AUC 0-48 (SD)	309.26 (105.542)	306.54 (114.674)	322.48 (101.045)	309.77 (103.511)	236.28 (97.872)
AUC 0-72 (SD)	434.05 (167.930)	430.11 (183.942)	460.17 (144.577)	428.15 (160.301)	351.46 (152.177)

Overall, these results suggest that bupivacaine HCl (50 mg), HTX-009 (3.6 mg of meloxicam alone) and HTX-002 (120 mg of bupivacaine alone) administered by injection have no or little analgesic effect according to mean AUC of pain intensity scores (AUC 0-24; AUC 0-48 and AUC 0-72) compared to placebo. Only HTX-011-56 (bupivacaine 120 mg / meloxicam 3.6 mg), all administration techniques combined, shows consistent numerical decrease of mean AUC of pain intensity scores (AUC 0-24; AUC 0-48 and AUC 0-72) compared to placebo. Assessment and extrapolation of these data seems difficult considering that administration techniques were pooled, effectives are relatively small, standard deviations are important and AUC for pain intensity scores collected over various time intervals was only included as an exploratory endpoint. In addition, it should be noted that HTX-011-56 (120 mg / 3.6 mg) is not the dose selected for the phase 3 study in bunionectomy.

The demonstration of the contribution of bupivacaine and meloxicam to the efficacy of Zynrelef (HTX-011) as, respectively, the active substance and the enhancer of activity without analgesic properties itself based on these data considered to be sufficient.

Herniorrhaphy: Study 202

"A Phase 2, Randomized, Pilot Study to Investigate the Safety, Efficacy, Pharmacokinetics and Bioavailability of HTX-011, HTX-002, or HTX-009 Administered Via Injection and/or Topical Application Following Unilateral Open Inguinal Herniorrhaphy".

This study was designed to evaluate the safety, efficacy, and PK of 3 HTX-011 formulations (HTX-011-19, HTX-011-49, and HTX-011-56) administered as a single dose via local administration into the surgical site using different administration techniques in adult subjects undergoing unilateral open inguinal herniorrhaphy.

Saline placebo and bupivacaine HCl 0.25% without epinephrine were used as controls. Two HTX-011-56 comparators, HTX-002 and HTX-009, were also included to evaluate the contribution of the APIs to the effects of HTX-011-56.

This study was used to determine the optimal formulation, dose, and method of administration for herniorrhaphy in phase 3.

The primary efficacy endpoint was the summed pain intensity score (SPI) over the first 24 hours (SPI0-24).

A total of 463 subjects were randomized and received study drug. 11 subjects did not complete the study. The main reason was lost to follow up. 16 subjects were randomized in HTX-011 300 mg / 9 mg administered by instillation group (the selected dose and administration technique for the phase 3 study).

Development of HTX-011-19 and HTX-011-49 was discontinued during the course of this study due to high viscosity for HTX-011-19 and to preliminary PK data for HTX-011-49.

The minimum effective dose that produced statistically significant reductions in SPI0-24 compared with bupivacaine HCl was HTX-011-56 300 mg/9 mg (primary endpoint). Moreover, the mean SPI0-24 was the lowest for HTX-011-56 300 mg/9 mg.

Administration of HTX-011-56 via injection generally did not result in improved mean pain intensity scores compared with saline placebo and bupivacaine HCl.

Mean plasma exposures of bupivacaine were generally similar across all administration techniques and no significant differences in plasma exposures of meloxicam were observed across the different administration techniques.

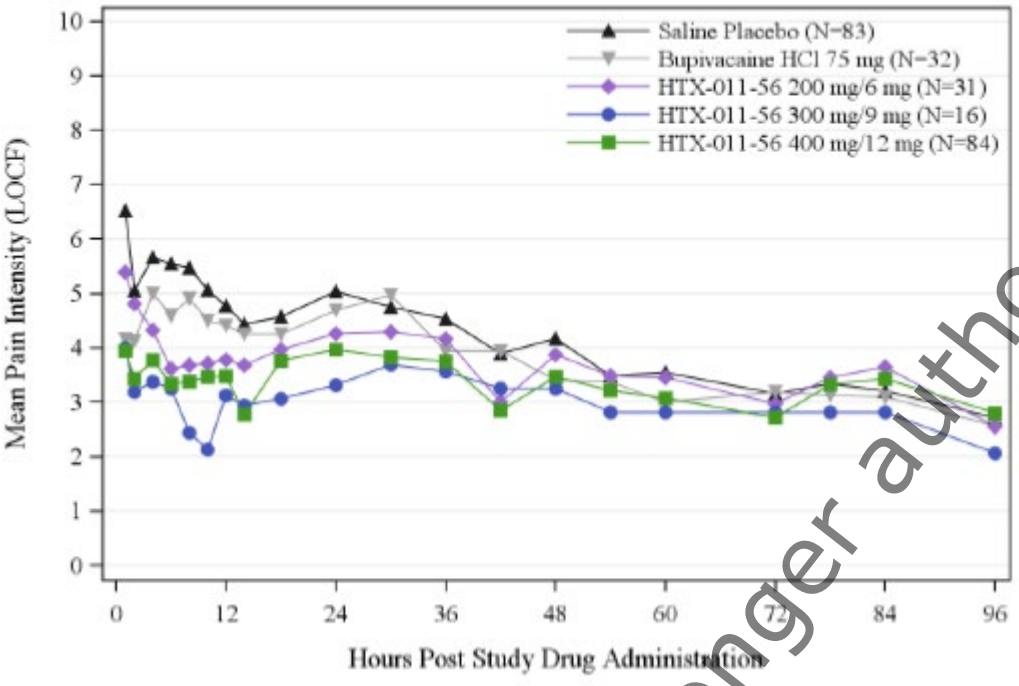
In order to select the phase 3 dose and formulation of HTX-011, the applicant has taken into account the formulation, dose, together with the administration technique to reduce postoperative pain with a favourable safety profile in subjects undergoing herniorrhaphy. As instillation is considered to be less invasive technique, the applicant determined that HTX-011-56 300 mg/9 mg via instillation using a Luer-lock applicator should be used for further clinical trial.

Table 12: Primary Efficacy Endpoint: Mean SPI0-24 for HTX-011-56 vs Saline Placebo and Bupivacaine HCl (LOCF, mITT Population)

Dose of HTX-011-56/ Administration Technique	N	Mean (SD)	Control	N	Mean (SD)	P-value
200 mg/6 mg Pooled[a]	31	97.16 (49.093)	PBO[b]	83	121.93 (48.239)	0.0168
			BPV	32	108.72 (37.552)	0.2971
300 mg/9 mg Instillation	16	73.81 (50.572)	PBO	83	121.93 (48.239)	0.0005
			BPV	32	108.72 (37.552)	0.0097
400 mg/12 mg Pooled[a]	84	86.61 (40.091)	PBO	83	121.93 (48.239)	<0.0001
			BPV	32	108.72 (37.552)	0.0080

Abbreviations: BPV, bupivacaine HCl; LOCF, last observation carried forward; mITT, modified Intent-to-Treat; PBO, saline placebo; SPI_{0-24}, summed pain intensity score over the first 24 hours.
Notes: p-values are from an analysis of variance (ANOVA). The results presented are for subjects with and without protocol-specified fentanyl administered at the end of the surgery and prior to administration of study drug (Parts B/C/D/E/F/G; treatment cohorts are presented in Section 9.1.2).
[a] Cohorts pooled for all administration techniques.
[b] Cohorts pooled for all administration techniques and dose volumes.
Source: Table 14.2.1.1.2

Figure 16: Mean Pain Intensity Scores over time for HTX-011-56 vs Saline Placebo and Bupivacaine HCl (LOCF, mITT Population)



Contribution of HTX-011 components to the reduction in mean AUC of pain Intensity Scores was assessed using least squares mean difference with HTX-011-56 400 mg/12 mg, HTX-002 400 mg and HTX-009 12 mg compared to placebo. HTX-011-56 400 mg/12 mg (administrated via instillation) reduced mean AUC of pain intensity scores more effectively than equivalent doses of either comparator: HTX-002 400 mg (administrated via instillation) or HTX-009 12 mg (administrated by a combination of injection and instillation). The reduction in pain intensity was more than the sum of the 2 comparators. According to the applicant, these findings show that the analgesic efficacy of HTX-011-56, a fixed-ratio combination product, is not the sole result of the disease-active component, bupivacaine.

An assessment of reduction in pain intensity was performed comparing HTX-011-56 against extended-release bupivacaine (HTX-002) and immediate-release bupivacaine (bupivacaine HCl).

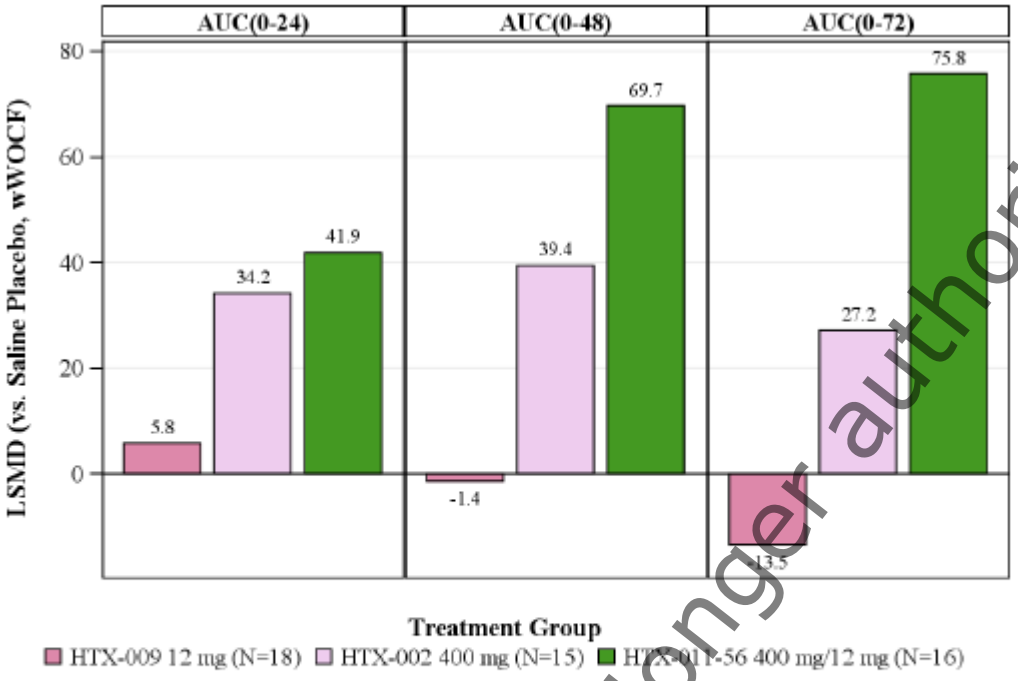
Table 13: Mean AUC of Pain Intensity Scores for HTX-011-56 vs HTX-002 (wWOCF, mITT Population)

	Administration techniques pooled		Instillation only		Administration techniques pooled		Instillation only		
	HTX-011-56 200 mg/6 mg (N = 31)	HTX-002 200 mg (N = 22)	HTX-011-56 200 mg/6 mg (N = 16)	HTX-002 200 mg (N = 13)	HTX-011-56 400 mg/12 mg (N = 46)	HTX-002 400 mg (N = 30)	HTX-011-56 400 mg/12 mg (N = 16)	HTX-002 400 mg (N = 15)	BPV 75 mg (N = 15)
AUC_{0-24}									
Mean (SD)	122.41 (59.940)	123.06 (42.543)	99.24 (50.486)	122.26 (43.163)	107.09 (57.559)	115.58 (55.810)	110.11 (65.379)	117.79 (63.243)	135.19 (56.062)
p-value vs HTX-002	0.9655		0.2041		0.5269		0.7422		
AUC_{0-48}									
Mean (SD)	241.17 (120.847)	261.15 (92.412)	192.84 (102.586)	263.45 (87.029)	217.29 (109.982)	232.95 (113.959)	220.10 (125.896)	250.36 (118.770)	272.41 (116.176)
p-value vs HTX-002	0.5177		0.0592		0.5514		0.4973		
AUC_{0-72}									
Mean (SD)	342.21 (167.960)	376.79 (141.213)	274.28 (130.981)	383.75 (130.390)	313.78 (165.283)	336.41 (178.204)	317.66 (189.382)	366.26 (171.896)	381.41 (175.658)
p-value vs HTX-002	0.4345		0.0333		0.5733		0.4614		

Abbreviations: AUC, area under the curve; BPV, bupivacaine HCl; mITT, modified Intent-to-Treat; wWOCF, windowed worst observation carried forward.
Notes: p-values are from an analysis of variance (ANOVA). Treatment cohorts are presented in Section 9.1.3.
Source: Table 14.2.5.3.2.

Overall, these results mostly suggest that the difference on mean AUC of pain intensity scores between HTX-011-56 (bupivacaine and meloxicam) and HTX-002 (bupivacaine only) is not obvious. The difference is statistically significant when HTX-011-56 200 mg/6 mg (N=16) is compared to HTX-002 200 mg (N=13) on mean AUC0-72 (both products were administrated by instillation). Although results may suggest a trend, the other differences are only numerical. Moreover, the effectives are too small and standard deviations are too high to draw firm conclusion.

Figure 17: Contribution of HTX-011 Components to the Reduction in Mean AUC of Pain Intensity Scores: HTX-011-56 400 mg/12 mg vs HTX-002 400 mg and HTX-009 12 mg (wWOCF, mITT Population)



Abbreviations: AUC, area under the curve; LSMD, least squares mean difference; mITT, modified Intent-to-Treat; wWOCF; windowed worst observation carried forward.
Note: HTX-002 and HTX-009 have similar compositions to HTX-011-56 except that HTX-002 contains only bupivacaine as the active pharmaceutical ingredient (API) and HTX-009 contains only meloxicam as the API. For HTX-011-56 400 mg/12 mg and HTX-002 400 mg, administration via instillation is presented. Treatment cohorts are presented in Section 9.1.2.
Source: Table 14.2.5.3.2.

Table 14: Mean AUC of pain intensity scores for placebo, bupivacaine HCl, HTX-002, HTX-009 and HTX-011-56 (wWOCF, mITT Population)

Mean AUC of pain intensity scores	Placebo (N=60) Injection + instillation	Bupivacaine HCl (50 mg) (N=15) Injection	HTX-002 (bupivacaine 400 mg) (N=15) Instillation	HTX-009 (meloxicam 12 mg) (N=18) Injection + instillation	HTX-011-56 (bupivacaine 400 mg / meloxicam 12 mg) (N=16) Instillation
AUC 0-24 (SD)	152.02 (54.284)	135.19 (56.062)	117.79 (63.243)	146.19 (35.860)	110.11 (65.379)
AUC 0-48 (SD)	289.81 (120.347)	272.41 (116.176)	250.36 (118.770)	291.19 (83.162)	220.10 (125.896)
AUC 0-72 (SD)	393.45 (184.664)	381.41 (175.658)	366.26 (171.896)	406.92 (137.347)	317.66 (189.382)

According to mean AUC of pain intensity scores (AUC 0-24; AUC 0-48 and AUC 0-72), HTX-009 (meloxicam 12 mg) shows no analgesic effect with numerical results close to placebo. Bupivacaine HCl (50 mg) presents very modest to no reduction of mean AUC of pain intensity scores (AUC 0-24; AUC 0-48 and AUC 0-72) compared to placebo. HTX-002 (bupivacaine 400 mg) reduces mean AUC of pain intensity scores (AUC 0-24; AUC 0-48 and AUC 0-72) compared to placebo. It should be noted that bupivacaine dose is 4 times higher in HTX-002 compared to bupivacaine HCl.

HTX-011-56 (bupivacaine 400 mg / meloxicam 12 mg) presents the higher reduction of mean AUC of pain intensity scores (AUC 0-24; AUC 0-48 and AUC 0-72) compared to placebo.

The interpretation of these results is limited due to small effect, high standard deviation, and the use of HTX-011-56 (bupivacaine 400 mg / meloxicam 12 mg) which is not the selected dose for the phase 3 study in herniorrhaphy. In addition, HTX-009 effect was assessed with pooled administration techniques. It is also difficult to understand how these differences on mean AUC of pain intensity scores (AUC 0-24; AUC 0-48 and AUC 0-72) will translate on patients pain experience.

The demonstration of the contribution of bupivacaine and meloxicam to the efficacy of Zynrelef (HTX-011) as, respectively, the active substance and the enhancer of activity without analgesic properties itself based on these data is endorsed, despite the study limitations.

Total Knee Arthroplasty: Study 209

"Phase 2b, Randomized, Double Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Infiltration for Postoperative Analgesia in Subjects Undergoing Total Knee Arthroplasty".

Study design

This study was designed to evaluate the analgesic efficacy, safety, and pharmacokinetics (PK) of HTX-011 administered as a single dose into the surgical site in subjects undergoing primary unilateral total knee arthroplasty (TKA).

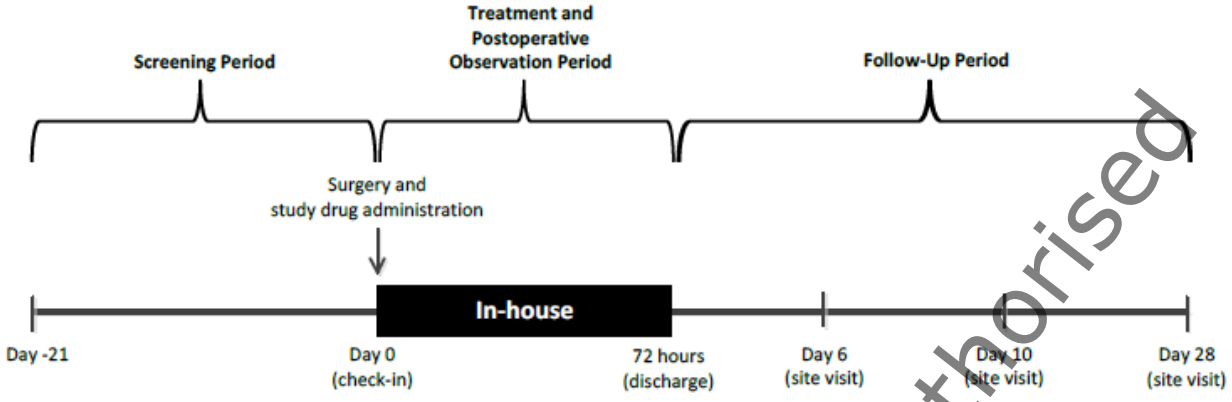
The study included 2 sequential cohorts. Cohort 1 was a dose- and administration technique-finding cohort and evaluated HTX-011 200 mg/6 mg administered via 2 different techniques (periarticular instillation or a combination of periarticular injection and instillation) compared with saline placebo and bupivacaine HCl 0.25% 125 mg. Cohort 2 evaluated HTX-011 400 mg/12 mg via periarticular instillation with or without a low-dose of ropivacaine (50 mg of a 0.5% solution) injected into the posterior capsule of the knee compared with saline placebo and bupivacaine HCl 0.25% 125 mg.

Cohort 2 was initiated after an interim review of Cohort 1 results by an unblinded internal Interim Review Committee (IRC).

Study drug was administered prior to the completion of surgery.

The study consisted in the following phases:

Figure 18



Study assessment

Efficacy assessments included evaluations of pain intensity using the Numeric Rating Scale of pain intensity score (NRS) at rest and with activity (NRS-R and NRS-A, respectively); use of opioid medication; the Patient Global Assessment (PGA) of pain control; assessments of rehabilitation, ambulation, and discharge readiness; the subject's satisfaction with postoperative pain control; and the subject's assessment of overall benefit of analgesia.

Safety assessments included adverse event (AE) recording, local anesthetic systemic toxicity (LAST) assessments, physical examinations, vital signs, electrocardiograms (ECGs) and Holter monitoring, motor function assessments, hematology and serum chemistry, and wound healing assessments.

PK assessments included the collection of blood samples at scheduled timepoints for bupivacaine and meloxicam PK analysis.

Main inclusion criteria

Subjects were male or female with scheduled unilateral TKA under general anesthesia and had not previously undergone TKA in either knee.

Main exclusion criteria

Subjects had another pre-existing painful condition that could confound pain assessments or were currently taking analgesics for a chronically painful condition, or had taken long-acting opioids within 3 days of surgery, or had taken any opioids within 24 hours of scheduled surgery for this study. Subjects had a known or suspected history of alcohol or drug abuse, or a positive drug screen. Subjects had clinically significant cardiac, renal or hepatic abnormalities.

Treatments

Cohort 1: Up to approximately 60 subjects were to be randomized to 1 of the following 4 treatment groups in a 2:2:1:1 ratio:

- HTX-011, 200 mg/6 mg (bupivacaine/meloxicam doses), 6.8 mL, via periarticular instillation into the surgical site
- HTX-011, 200 mg/6 mg (bupivacaine/meloxicam doses), 6.8 mL, via a combination of periarticular injection and instillation into the surgical site
- Saline placebo, 6.8 mL, via periarticular injection into the surgical site
- Bupivacaine HCl without epinephrine 0.25%, 125 mg (50 mL), via periarticular injection into the surgical site

Cohort 2: Up to approximately 200 subjects were to be randomized to 1 of the following 4 treatment groups in a 1:1:1:1 ratio:

- HTX-011, 400 mg/12 mg (bupivacaine/meloxicam doses), 13.7 mL, via periarticular instillation into the surgical site
- HTX-011, 400 mg/12 mg (bupivacaine/meloxicam doses), 13.7 mL, via periarticular instillation into the surgical site, and ropivacaine 0.5% (50 mg, 10 mL) via periarticular injection into the surgical site (posterior capsule)
- Saline placebo, 13.7 mL, via periarticular injection into the surgical site
- Bupivacaine HCl without epinephrine 0.25%, 125 mg (50 mL), via periarticular injection into the surgical site

The surgical procedure was conducted under general anesthesia or spinal anesthesia.

In cohort 1, subjects received a standardized 50 µg of IV fentanyl after study drug administration and before wound closure to minimize the inherent variability of intraoperative pain control on immediate postoperative pain. After an amendment, the amount of IV fentanyl administered intraoperatively was increased to 75 µg.

In cohort 2, all subjects were administered pregabalin orally (PO; 150 mg) and acetaminophen intravenously (IV; ≤1,000 mg in a 6-hour window, as per the approved prescribing information) just prior to surgery to reduce initial postoperative pain. The subjects also received a standardized 75 µg of IV fentanyl after study drug administration and before wound closure

Rescue medication during 72 hours after study drug administration was allowed to subjects with inadequately controlled pain symptoms. The rescue medications were the following:

- Morphine up to 15 mg IV for the first 2 hours;
- Thereafter, morphine up to 10 mg IV in a 2-hour period;
- Oral oxycodone up to 10 mg within any 4-hour period as needed

After 72 hours, the analgesic regimen could be adjusted for each subject individually as deemed appropriate by the physician responsible for the postoperative care.

Main study objectives

Primary: to compare the efficacy and duration of analgesia achieved following periarticular infiltration of HTX-011 with that of saline placebo in subjects undergoing unilateral TKA.

Main secondary objectives:

- To compare the efficacy and duration of analgesia for HTX-011 with that of bupivacaine HCl without epinephrine in this study population;
- To evaluate additional efficacy parameters, including opioid load, in this study population;
- To evaluate the efficacy and duration of analgesia for HTX-011 administered using different techniques in this study population.

Main efficacy endpoints

The primary efficacy endpoint was the mean AUC of the NRS-R pain intensity scores through 48 hours (AUC0-48).

The key secondary endpoint was the mean AUC of the NRS-R pain intensity scores through 72 hours (AUC0-72).

Main secondary endpoints included mean total postoperative opioid consumption (in morphine equivalents) through 24, 48, and 72 hours, median time in hours to first opioid rescue administration and mean NRS-R and mean NRS-A pain intensity scores at each assessed timepoint.

Study subjects

A total of 285 subjects were randomized and received study drug, 63 in Cohort 1 and 222 in Cohort 2. The numbers of male and female subjects within each cohort were evenly distributed. The mean age was 61.9 (8.06) years in Cohort 1 and 62.1 (8.90) years in Cohort 2. Over 98% of subjects in each cohort completed the study.

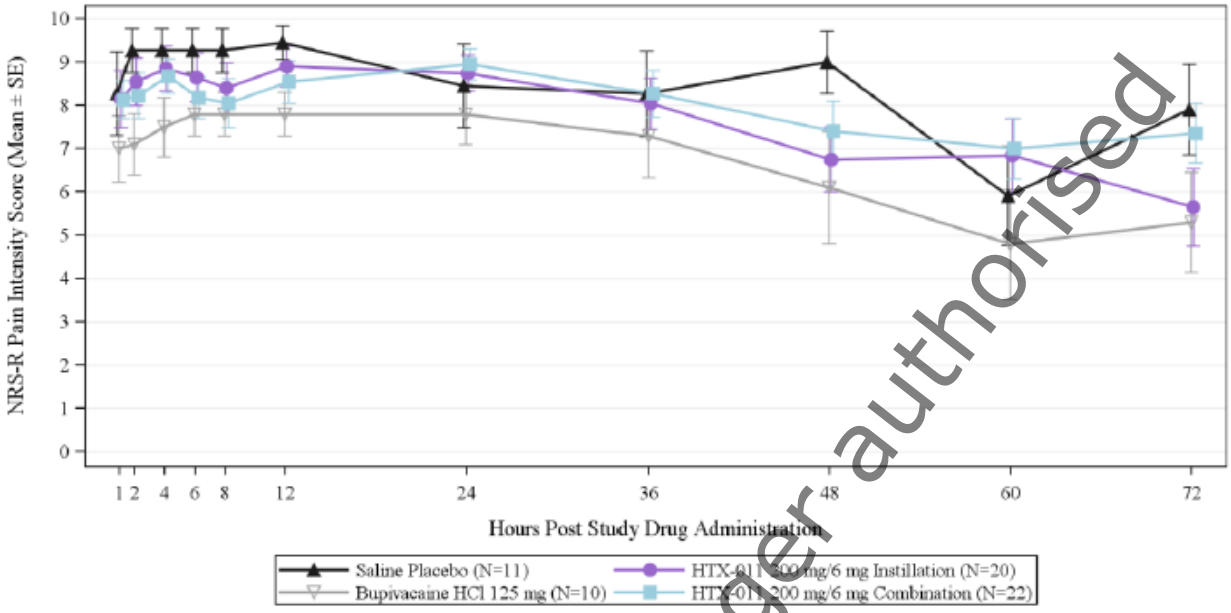
Main Results in cohort 1

Efficacy appeared to be similar for both HTX-011 200 mg/6 mg groups, instillation and combination of instillation and injection. Both HTX-011 200 mg/6 mg groups had numerically lower mean AUC0-48 of NRS-R pain intensity scores (primary endpoint) and mean AUC0-72 of NRS-R pain intensity scores (key secondary endpoint) compared with saline placebo (primary comparison), but the treatment group differences did not reach statistical significance. In addition, total opioid consumption was lower in both HTX-011 200 mg/6 mg groups through 24, 48, and 72 hours (other secondary endpoints) compared with saline placebo.

Both HTX-011 200 mg/6 mg groups had higher mean pain intensity scores compared with the bupivacaine HCl group; however, the treatment differences in the mean NRS-R scores at 24, 48, and 72 hours, as well as the mean AUC0-48 and AUC0-72 of NRS-R pain intensity scores, were not statistically significant. Total opioid consumption for the bupivacaine HCl group was lower than or similar to the HTX-011 groups through 24, 48, and 72 hours.

These results suggested there was some clinical activity with HTX-011, but that the dose, 200 mg/6 mg, was likely not high enough.

Figure 19: Mean NRS-R Pain Intensity Scores over Time for Cohort 1 (wWOCF, ITT Population)



Abbreviations: ITT, Intent-to-Treat; NRS-R, Numeric Rating Scale of pain intensity score at rest; wWOCF, windowed worst observation carried forward.
Source: Figure 14.2.3.1.

Table 15: Mean AUC0-48 and AUC0-72 of NRS-R Pain Intensity Scores (wWOCF, ITT Population)

	Saline Placebo (N=11)	Bupivacaine HCl 125 mg (N=10)	HTX-011 200 mg/6 mg Instillation (N=20)	HTX-011 200 mg/6 mg Combination[a] (N=22)
Mean AUC_{0-48} of NRS-R				
Mean (SD)	405.82 (97.549)	347.56 (103.422)	386.12 (82.930)	391.56 (84.450)
p-value vs saline placebo			0.5594	0.6674
p-value vs bupivacaine HCl			0.2702	0.2020
Mean AUC_{0-72} of NRS-R				
Mean (SD)	576.44 (150.815)	468.58 (179.687)	543.14 (142.566)	560.85 (136.099)
p-value vs saline placebo			0.5513	0.7764
p-value vs bupivacaine HCl			0.1986	0.1076

Abbreviations: AUC, area under the curve; ITT, Intent-to Treat; NRS-R, Numeric Rating Scale of pain intensity score at rest; wWOCF, windowed worst observation carried forward.
Notes: p-values reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect.
[a] Combination refers to half the volume of HTX-011 administered via periarticular injection and half administered via instillation.
Sources: Table 14.2.1.1.1, Table 14.2.1.5.1.

Table 16: Total Postoperative Opioid Consumption (MME) From 0 through 24, 48, and 72 Hours in Cohort 1 (ITT Population)

	Saline Placebo (N=11)	Bupivacaine HCl 125 mg (N=10)	HTX-011 200 mg/6 mg	
			Instillation (N=20)	Combination[a] (N=22)
Opioid consumption through 24 hours				
Mean (SD)	37.14 (9.910)	33.50 (15.188)	32.10 (11.512)	31.86 (15.183)
Median (Min, Max)	37.00 (25.0, 52.0)	28.50 (14.5, 60.0)	33.50 (5.0, 53.0)	30.25 (5.0, 69.5)
p-value vs saline placebo			0.3855	0.2356
p-value vs bupivacaine HCl			0.9473	0.9028
Opioid consumption through 48 hours				
Mean (SD)	56.05 (12.982)	50.15 (22.642)	50.63 (21.581)	51.89 (23.511)
Median (Min, Max)	56.00 (30.0, 74.0)	49.50 (20.0, 84.0)	48.00 (21.0, 98.0)	46.25 (5.0, 117.5)
p-value vs saline placebo			0.4953	0.3204
p-value vs bupivacaine HCl			0.9824	0.9190
Opioid consumption through 72 hours				
Mean (SD)	70.41 (18.057)	60.70 (29.903)	65.53 (31.615)	66.86 (31.154)
Median (Min, Max)	73.00 (32.5, 94.0)	57.00 (21.0, 104.0)	60.50 (26.0, 125.0)	63.75 (5.0, 147.5)
p-value vs saline placebo			0.6796	0.4335

The result for TKA study for cohort 1 was negative regarding the selected primary endpoint. HTX-011 200 mg/6 mg did not produce significantly superior pain relief compared with the control groups. However, the applicant considered that there was an indication of activity, based only on numerically lower NRS-S pain intensity scores and total opioid consumption compared with saline placebo.

In that context, the applicant decided to proceed to Cohort 2 with a higher dose level of HTX-011 (400mg/12mg), based on the hypothesis that the dose of 200mg/6mg was not high enough.

The applicant chose the method of administration for HTX-011 in Cohort 2 to parallel the administration technique in the phase 3 studies. Instillation was therefore adopted for Cohort 2.

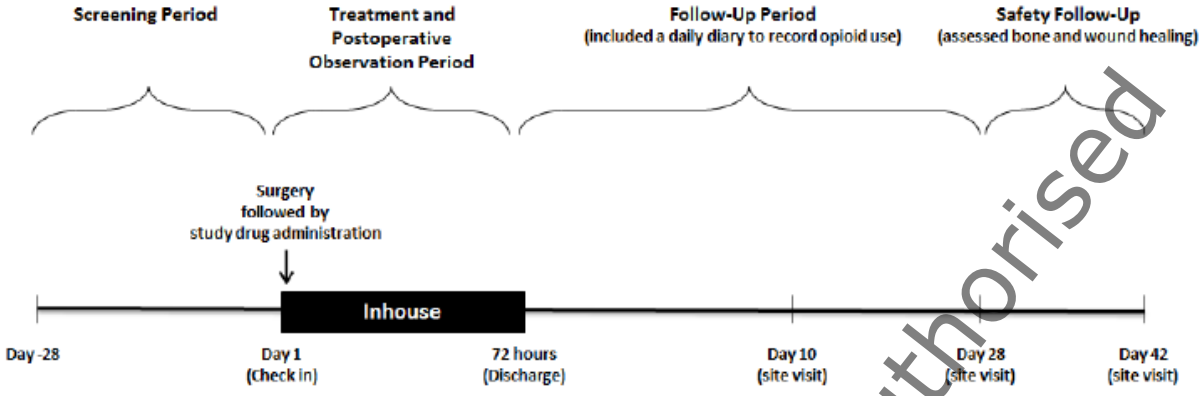
2.5.2. Main study(ies)

A Phase 3, Randomized, Double-Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Local Administration for Postoperative Analgesia and Decreased Opioid Use Following Unilateral Simple Bunionectomy

Methods

The study consisted in the following phases:

Figure 20



Study Participants

Main inclusion criteria

Each subject had to meet all of the following criteria to be enrolled in this study:

1. Was male or female, and ≥18 years of age at screening.

2. Was scheduled to undergo a primary unilateral, distal, first metatarsal bunionectomy with osteotomy and internal fixation under regional anesthesia.

3. Had an American Society of Anesthesiologists Physical Status of I, II, or III.

Main exclusion criteria

Subjects who met any of the following criteria were excluded from the study:

1. Had a contralateral foot bunionectomy in the past 3 months.

2. Had a planned concurrent surgical procedure (e.g., bilateral bunionectomy or collateral procedures on the surgical foot).

3. Had a pre-existing concurrent acute or chronic painful physical/restrictive condition expected to require analgesic treatment in the postoperative period for pain that was not strictly related to the bunionectomy and which may confound the postoperative assessments.

4. Had a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction to bupivacaine (or other local anesthetics), meloxicam (or other NSAIDs), oxycodone, morphine, or acetaminophen.

5. Had known or suspected daily use of opioids for 7 or more consecutive days within the previous 6 months.

6. Had taken NSAIDs (including meloxicam) within 10 days prior to the scheduled surgery with the exception of subjects on low dose (≤100 mg) daily acetylsalicylic acid for cardioprotection.

7. Had taken long-acting opioids within 3 days prior to the scheduled surgery.

8. Had taken any opioids within 24 hours prior to the scheduled surgery.

9. Had been administered bupivacaine within 5 days prior to the scheduled surgery.

10. Had been administered any local anesthetic within 72 hours prior to the scheduled surgery, other than for pretreatment prior to a needle placement, to treat an AE that occurs after signing the ICF, or to decrease venous irritation (e.g., caused by propofol, in which case no more than a single administration of lidocaine 1% 20 mg IV could be administered).

11. Had initiated treatment with any of the following medications within 1 month prior to study drug administration or was taking any of these medications to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, or cyclooxygenase-2 (COX-2) inhibitors. Anxiolytics prior to surgery were permitted, if necessary.

12. Had been administered systemic steroids within 5 half-lives or 10 days prior to administration of study drug (whichever was longer).

13. Had a medical condition such that, in the opinion of the Investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments.

14. Had a known or suspected history of drug abuse, a positive drug screen on the day of surgery, or a recent history of alcohol abuse.

Overall, inclusion and exclusion criteria are adequate. However, the study population does not represent target population where pre-existing concurrent acute or chronic painful conditions, opioid medication use and/or drug abuse (opioids) could be rather common. These excluded conditions represent patients with risk factors that could be more difficult to treat. This should be kept in mind for the analysis of the effect size.

Treatments

The study population was randomized into three treatment groups in a 3:3:2 pattern generated by computer as follows:

- HTX-011, 60 mg/1.8 mg (2.1 mL) via instillation into the surgical site using a Luer lock applicator.
- Bupivacaine HCl without epinephrine 0.5%, 50 mg (10 mL), via injection into the surgical site.
- Saline placebo (2.1 mL) via instillation into the surgical site using a Luer lock applicator.

The surgical procedure was performed under regional anesthesia with no more than 20 mL of 1% lidocaine without epinephrine administered as a Mayo block. During surgery, the use of intravenous (IV) fentanyl up to 4 µg/kg was permitted for intraoperative pain control.

Rescue medication

Postoperative rescue medication consisted of oral (PO) immediate-release oxycodone (no more than 10 mg within a 4-hour period as needed), IV morphine (no more than 10 mg within a 2-hour period as needed), and/or oral acetaminophen (no more than 1,000 mg in a 6-hour period). Rescue medication was administrated upon request.

At discharge, subjects were to be provided a daily diary to record if they took any opioid medication from 72 hours through Day 28 (yes or no).

Objectives

Primary objective:

To compare the efficacy and duration of analgesia following local administration of HTX-011 with saline placebo during the first 72 hours following unilateral simple bunionectomy.

Secondary objectives:

- To compare the efficacy and duration of analgesia for HTX-011 with bupivacaine HCl without epinephrine during the first 72 hours following surgery.
- To compare the effect of HTX-011 with saline placebo and bupivacaine HCl without epinephrine on opioid load during the first 72 hours following surgery.
- To assess the safety and tolerability of HTX-011.
- To further establish the PK parameters of bupivacaine and meloxicam in HTX-011.

Outcomes/endpoints

Primary Endpoint

Mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) through 72 hours (AUC0-72) for HTX-011 compared with saline placebo.

Key secondary endpoints

- Mean AUC0-72 of the NRS-A pain intensity scores for HTX-011 compared with bupivacaine HCl.
- Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with saline placebo.
- Proportion of subjects who are opioid-free through 72 hours for HTX-011 compared with bupivacaine HCl.
- Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with bupivacaine HCl.

Other secondary endpoints

- Proportion of subjects who are opioid-free through 72 hours compared with saline placebo.
- Proportion of subjects who are opioid-free from 72 hours through Day 10 and Day 28.
- Median time in hours to first opioid rescue medication up to 72 hours.
- Mean AUC0-72 of the NRS-R pain intensity scores.
- Integrated Rank Analysis of Silverman using the NRS-A pain intensity AUC scores and total opioid consumption through 72 hours.
- Proportion of subjects who are pain-free with activity (defined as an NRS-A pain intensity score of 0 or 1) at each assessed timepoint through Day 28.
- Proportion of subjects with an NRS-A pain intensity score ≥4 at any timepoint through 72 hours.
- Proportion of subjects with an NRS-A pain intensity score ≥7 at any timepoint through 72 hours.
- Proportion of subjects who first achieve an MPADSS score ≥9 at 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours.
- Proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA at 24, 48, 72 hours, and on Day 28.

Pain intensity assessments

Subjects were asked to evaluate their current pain level at scheduled timepoints after surgery. Pain intensity scores were assessed using an 11-point NRS (0–10) where 0 represented "no pain" and 10 represented "worst pain imaginable" (Breivik 2008). NRS scores were recorded first at rest (NRS-R) and then with activity (NRS-A).

For NRS-R assessments, subjects were seated/recumbent with the surgically attended leg elevated or lying supine. Measurements were obtained after the subject was in the resting position for at least 5 minutes.

For NRS-A assessments, subjects were seated with the plantar surface of the ball of the surgically attended foot touching the floor (no weight-bearing).

Pain intensity assessments were scheduled at 1, 2, 4, 8, 12, 24, 36, 48, 60, 72 hours and at D10 and D28 post-dose.

Patient global assessment of pain control

Subjects were asked to evaluate their pain control over the preceding 24 hours using a 4-point PGA scale where 0 represented "poor" and 3 represented "excellent" (Rothman 2009).

Scheduled timepoints were: 24, 48, 72 hours and D28 post-dose.

NRS-A was selected for the primary and first key secondary endpoints because NRS is known to be a sensitive measure of pain control after surgery, and effective relief of acute pain with activity is considered clinically meaningful as it facilitates mobilization and may therefore improve long-term outcome after surgery. The prescribed activity reflects a simple daily activity for patients: sitting with the plantar surface of the ball of the surgically attended foot touching the floor (no weight-bearing).

The timepoint of 72 hours selected for the primary and key secondary endpoints in this study is considered by the applicant clinically relevant for patients as literature shows that the most severe postoperative pain occurs within the first 72 hours after surgery.

Sample size

Sample size was determined by the applicant based on the estimate of the following parameters from a previous phase 2 study in subjects undergoing unilateral simple bunionectomy:

Table 17

Parameter	Saline Placebo	Bupivacaine HCl	HTX-011 60 mg/1.8 mg
Pain intensity AUC_{0-72}: Mean (SD)	425 (175)	425 (175)	325 (175)
Opioid consumption (mg): Mean (SD)	30 (25)	30 (25)	20 (20)
Proportion of opioid-free subjects	5%	10%	25%

Approximately 400 subjects (150 subjects in the HTX-011 group, 150 subjects in the bupivacaine HCl active control group, and 100 subjects in the saline placebo control group) were planned to be randomized to provide at least 90% power to detect a statistically significant difference (2-sided alpha=0.05) between the HTX-011 group and each of the control groups for each of the primary and key secondary endpoints.

Randomisation and blinding (masking)

The study population was randomized into three treatment groups in a 3:3:2 pattern. The site's pharmacy and surgical staff were not blinded to the treatment assignments because HTX-011 is a colored, viscous substance and is therefore distinguishable from both bupivacaine HCl and saline placebo. However, subjects were not aware of the study drug they received, and once surgery was completed and the subject was transferred to the PACU, the Investigator and all site staff involved in safety and efficacy assessments were blinded to the treatment assignment until after database lock.

Statistical methods

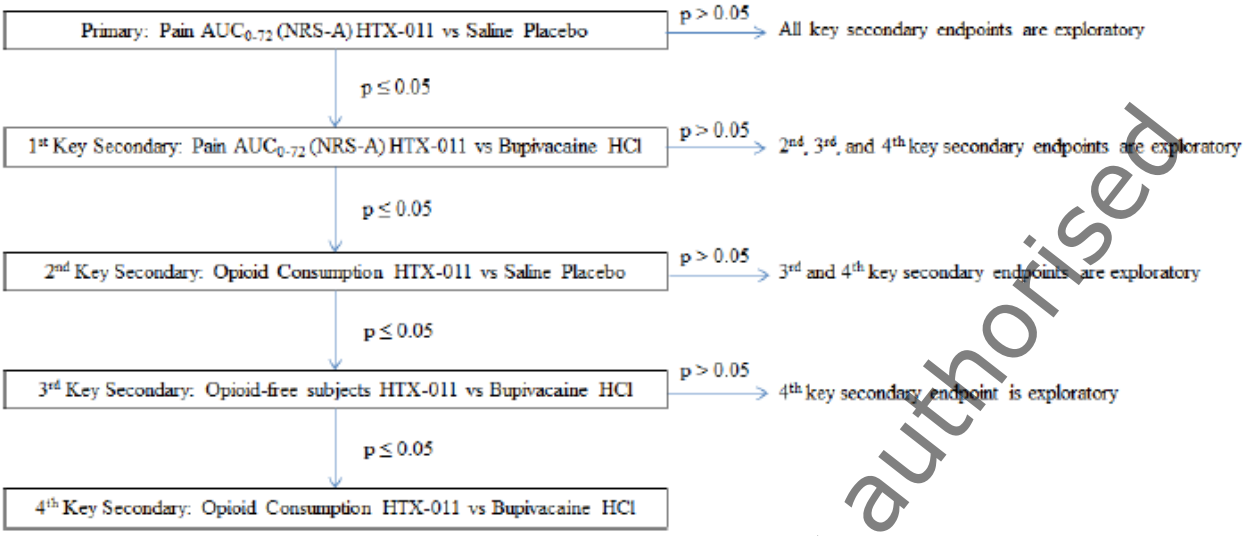
Analysis populations

- Intent-to-Treat (ITT) Population: All subjects who were randomized and received study drug were included in the ITT Population.
- Per Protocol Population: All subjects in the ITT Population who did not receive a prohibited rescue medication prior to 72 hours and who had no important protocol violations prior to 72 hours were included in the Per Protocol Population.
- Safety Population: All subjects who received study drug were included in the Safety Population.

The primary and first key secondary endpoints were analysed using analysis of variance with treatment group as the main effect, together with pairwise t tests to analyse differences between treatment groups. Missing data, which were expected to be very low due to the 72 hours hospitalization following surgery, were imputed via last observation carried forward for interval censored pain intensity scores and worst observation carried forward (WOCF) for right-censored pain intensity scores in the intent-to-treat (ITT) population. To adjust for the analgesic effect of opioid rescue medication, the windowed WOCF method was implemented as the primary analysis method in which pain intensity scores observed during the analgesic window of any opioid rescue medication were replaced with the worst post-dose, non-missing NRS pain intensity score observed prior to the rescue medication window. A sensitivity analysis of the primary endpoint was performed with no adjustment for opioid usage. The total postoperative opioid consumption through 72 hours was analyzed using a Wilcoxon rank-sum test. The proportion of subjects who were opioid free through 72 hours was analyzed using Fisher's exact test.

In order to account for multiple hypothesis testing on the primary endpoint and on each of the 4 key secondary endpoints, a testing hierarchy was applied to control study-wise alpha level at 0.05.

Figure 21: Hierarchical Test Procedure for Primary and Key Secondary Endpoints

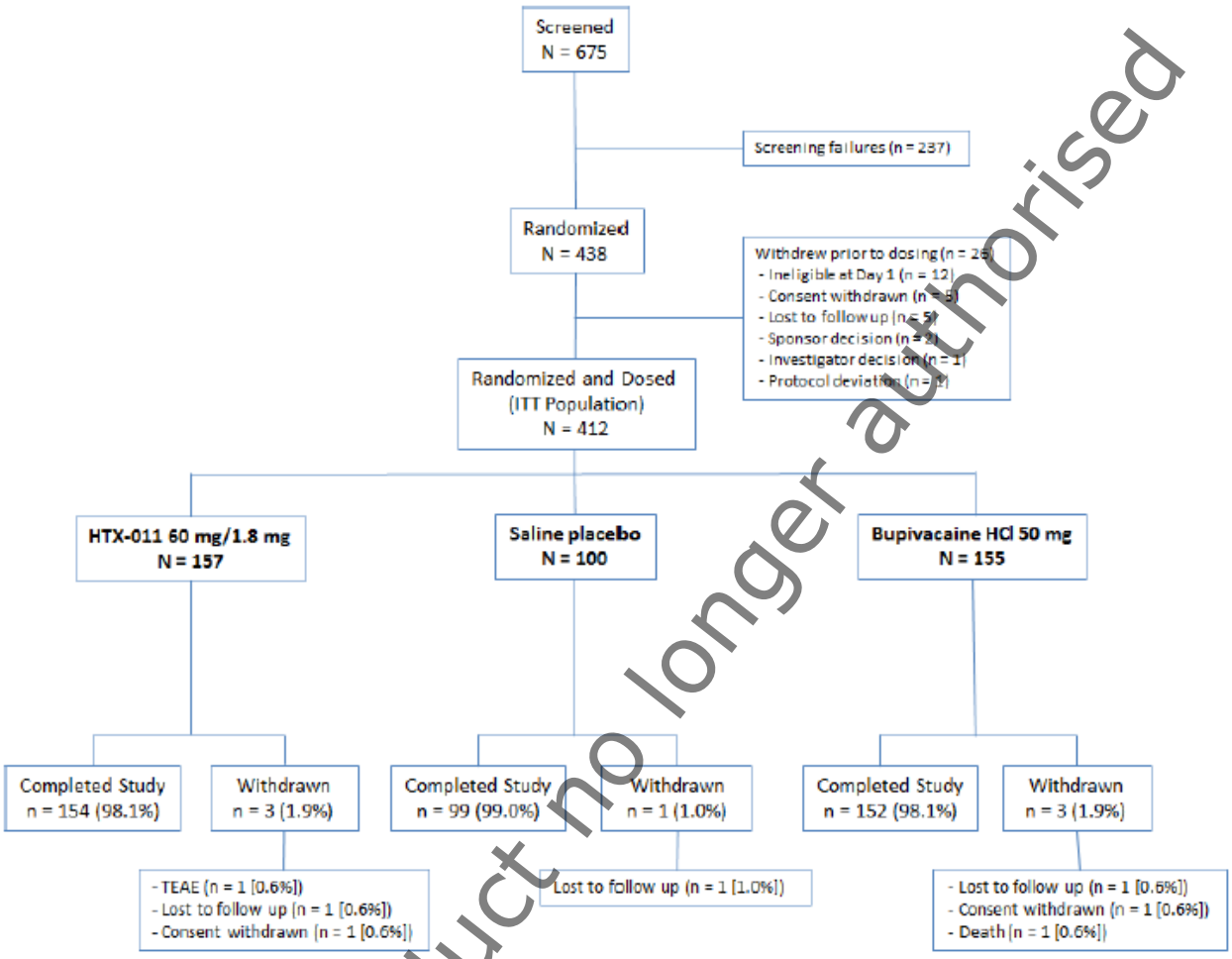


Abbreviations: AUC_{0-72}, area under the curve from Time 0 through 72 hours; NRS-A, Numeric Rating Scale of pain intensity score with activity.

Windowed worst observation carried forward (wWOCF) was used to adjust the NRS-A through 72 hours scores for the duration effect of opioid rescue medications. However, wWOCF was not used to adjust scores for the duration of effect of non-opioid recue medications (acetaminophen).

Results

Figure 22: Participant flow



Abbreviations: ITT, Intent-to Treat; TEAE, treatment-emergent adverse event.
Notes: Screened was defined as signing an informed consent form. Completed the study was defined as completing the Day 42 Safety Follow-Up Visit. One subject randomized to the bupivacaine HCl group was misdosed; the subject received saline placebo instead of bupivacaine HCl.

Baseline data

The overall study population was predominantly female (86.4%). The mean (SD) age was 46.9 (14.22) years, ranging from 18 to 77 years, and the mean BMI (SD) was 27.4 (4.70) kg/m2. The study subjects were overall well balanced across treatment's groups. The etiology of hallux valgus may be multifactorial. Main risk factors are: age, heredity, wearing of high heel and narrow shoes. In about 90% of cases, hallux valgus began between 40 and 50 years old and affects women. Regarding median age and sex ratio, it is considered that study population correctly reflects general population affected by hallux valgus.

Numbers analysed

Table 18: Number of Subjects per Analysis Population

Analysis Populations	HTX-011 60 mg/1.8 mg	Saline Placebo	Bupivacaine HCl 50 mg	Total
Randomized	164	109	165	438
ITT	157	100	155	412
Safety	157	101[a]	154[a]	412
Per Protocol	142	83	138	363

Abbreviation: ITT, Intent-to-Treat.
Notes: The ITT Population included all subjects who were randomized and received study drug. The randomized treatment assignment was used for analysis the ITT Population. The Safety Population included all subjects who received study drug. The actual treatment received was used for analysis in the Safety Population. The Per Protocol Population included all subjects in the ITT Population who did not receive a prohibited rescue medication prior to 72 hours and who had no important protocol deviations prior to 72 hours.
[a] One subject was randomized to bupivacaine HCl, but received saline placebo.
Source: Table 14.1.1.1.

Outcomes and estimation

Primary endpoint and first secondary endpoint: Mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) through 72 hours (AUC0-72)

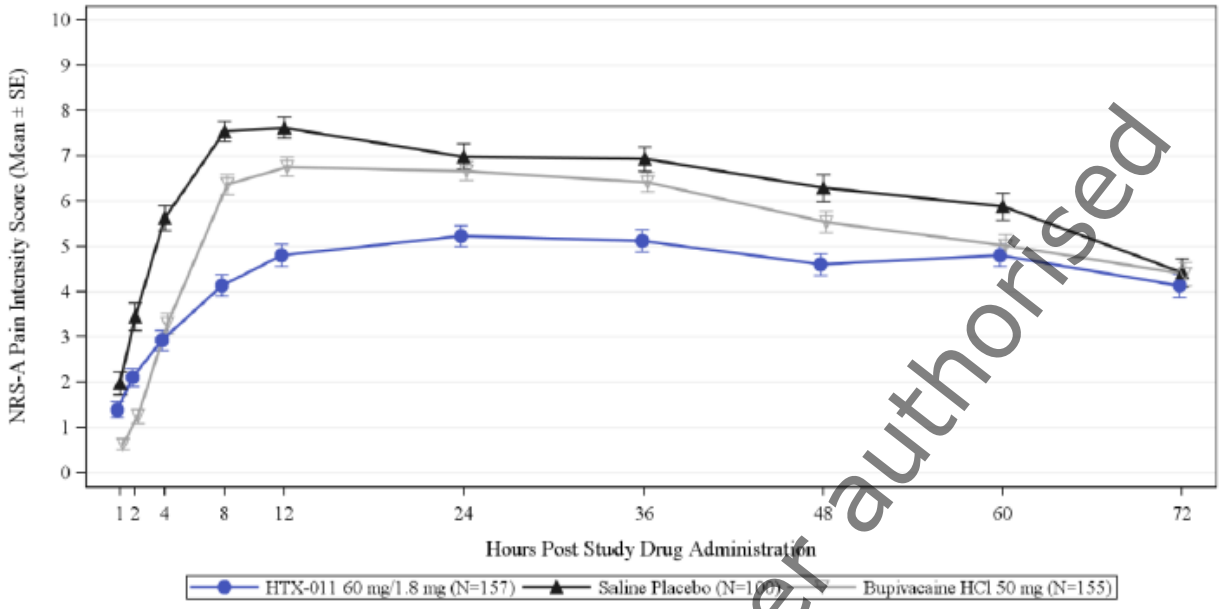
Table 19: Mean AUC0-72 of the NRS-A Pain Intensity Scores for HTX-011 vs Saline Placebo and Bupivacaine HCl (wWOCF, ITT Population)

	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=100)	Bupivacaine HCl 50 mg (N=155)
AUC_{0-72}			
Mean (SD)	323.29 (182.641)	445.34 (155.792)	393.45 (153.756)
LSMD (SE) [95% CI] vs saline placebo	-122.05 (21.217) [-163.76, -80.34]		
p-value vs saline placebo	<0.0001		
LSMD (SE) [95% CI] vs bupivacaine HCl	-70.16 (18.777) [-107.07, -33.25]		
p-value vs bupivacaine HCl	0.0002		

Abbreviations: AUC_{0-72}, area under the curve from Time 0 through 72 hours; ITT, Intent-to-Treat; LSMD, least squares mean difference; NRS-A, Numeric Rating Scale of pain intensity score with activity; wWOCF, windowed worst observation carried forward.
Note: p-values reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect.
Source: Table 14.2.1.1.

The mean AUC0-72 of the NRS-A pain intensity score was lower in the HTX-011 group compared with saline placebo (primary endpoint) and compared with bupivacaine HCl (first key secondary endpoint) and the differences are statistically significant.

Figure 23: Mean NRS-A Pain Intensity Scores over time (wWOCF, ITT Population)



Abbreviations: ITT, Intent-to-Treat; NRS-A, Numeric Rating Scale of pain intensity score with activity; wWOCF, windowed worst observation carried forward.
Source: Figure 14.2.7.

With the exception of the first 2 hours after study drug administration, where mean NRS-A pain intensity scores is lower in the bupivacaine group, HTX-011 presents lower NRS-A pain intensity scores compared with saline placebo and bupivacaine groups through 72 hours. As surgery was performed under regional anesthesia with a lidocaine Mayo block, which provides several hours of analgesia, this explains the low pain scores across groups in this first hours post-dose in this study.

These results show a statistically significant reduction of mean AUC0-72 of the NRS-A pain intensity score in the HTX-011 group compared with saline placebo and bupivacaine HCl groups. However, the clinically relevant difference for comparing the mean AUC0-72h of pain intensities has not been discussed or justified. As a consequence, clinical translation of obtained results in AUC are difficult to extrapolate and are open to interpretation. The applicant proposed a justification of the clinical significance based on a 10% to 20% reduction in NRS pain intensity scores as a minimal clinically important difference (MCID) defined by The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) in chronic pain. However, when AUC of pain intensity scores has been X% decreased in the Zynrelef group compared to the "reference" AUC in the placebo group at a precise time point does not mean that pain has been X% reduced. The minimal decrease in AUC of pain scores that would translate to a minimal decrease in pain that would been considered as clinically significant is not defined.

Second and fourth key secondary endpoints: Mean total postoperative opioid consumption (in intravenous mg morphine equivalents, MME) through 72 hours

Table 20: Total Postoperative Opioid Consumption (MME) through 72 Hours for HTX-011 vs Saline Placebo and Bupivacaine HCl (ITT Population)

	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=100)	Bupivacaine HCl 50 mg (N=155)
Total Opioid Consumption Through 72 Hours			
Mean (SD)	18.80 (19.801)	30.06 (21.016)	25.09 (21.553)
Median (Min, Max)	12.50 (0.0, 83.0)	25.00 (0.0, 80.0)	17.50 (0.0, 92.5)
p-value vs saline placebo	<0.0001		
p-value vs bupivacaine HCl	0.0022		

Abbreviations: ITT, Intent-to-Treat; MME, morphine milligram equivalent.
Notes: Opioid rescue medication included morphine and oxycodone. P-values were obtained using the Wilcoxon rank sum test.
Source: Table 14.2.2.1.

Total opioid consumption through 72 hours was lower in the HTX-011 group compared with saline placebo and bupivacaine HCl groups. The differences between median consumptions of opioids through 72 hours are statistically significant.

However, the intragroup differences between the minimal and the maximal consumption are high and similar between treatment groups (from 0 to 80/90 MME in each group). Numerically, the mean and median differences between the groups, in particular between HTX-011 and bupivacaine HCl groups seem modest. In HTX-011 group, over 72 hours, mean total opioid consumption is reduced by 37% compared with saline placebo and by 25% compared with bupivacaine HCl. The applicant justified the clinical significance of the opioid sparing effect in particular for outcomes in patients, with an overall reduction of prespecified ORAEs with HTX-011 compared to saline placebo and bupivacaine: 43.9% vs 53.5% vs 50.6% respectively.

It is endorsed that HTX-011 allowed an opioid sparing effect of about 6 to 7 of morphine mg equivalent in the first 24 hours compared to placebo which is under what seems to be possibly achieved with other analgesics such as paracetamol and NSAIDs. These 6 to 7 morphine mg equivalent sparing achieved in the first 24 hours is the most important sparing effect achieved on the overall interval of 72 hours (about 50% of the total opioid sparing). It could be hypothesized that the opioid sparing effect on the overall interval (0-72 hours) may be mainly driven by the opioid sparing effect on the first day post-dose (0-24 hours). Overall, the applicant successfully justified an opioid sparing effect associated with a decrease in ORAE. The estimation of the effect size is limited by the study design. Indeed, patient controlled analgesia (PCA) appears to be the method of choice to estimate opioid sparing effect because an accurate measure of postoperative opioids needs should be preferably based on a method where patients can "freely" access to opioids to relieve pain and accept some degree of undesirable effects. In addition, to a lesser extent, effect is limited by the use of paracetamol but its influence on opioid sparing is considered limited because the proportion of subjects who used paracetamol was overall lower in the HTX-011 group ad mean total use of paracetamol and average daily use were similar or lower in HTX-011 compared to the two other groups. This opioid sparing effect of HTX-011 is considered as modest but clinically significant.

Third key secondary and other endpoint: proportion of subjects who are opioid-free through 72 hours

Table 21: Proportion of Subjects Who are Opioid-Free through 72 Hours for HTX-011 vs Saline Placebo and Bupivacaine HCl (ITT Population)

	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=100)	Bupivacaine HCl 50 mg (N=155)
Subjects Who Are Opioid-Free Through 72 Hours	45 (28.7%)	2 (2.0%)	17 (11.0%)
Difference (95% CI) vs saline placebo	26.7% (18.6%, 34.7%)		
p-value vs saline placebo	<0.0001		
Difference (95% CI) vs bupivacaine HCl	17.7% (8.5%, 26.5%)		
p-value vs bupivacaine HCl	0.0001		

Abbreviation: ITT, Intent-to-Treat.
Notes: Opioid-free through 72 hours was defined as subjects who had total MME opioid dose of 0 through 72 hours. P-values were derived using Fisher's exact test. Exact 95% CI was based on Farrington-Manning score statistics.
Source: Table 14.2.3.1.

The proportion of subjects who did not require any opioid rescue medication over the 72-hour postoperative period was higher in the HTX-011 group compared with bupivacaine HCl (3rd key secondary endpoint) and compared with saline placebo (other secondary endpoint). The differences are statistically significant.

Sensitivity analyses

The applicant proposes sensitivity analyses performed on the primary and first key secondary endpoints to support the robustness of the primary analyses. Results of mean AUC0-72 of NRS-A pain intensity scores are presented without adjusting for opioid use and also using adjustment for opioid use in the per protocol population.

Table 22: Sensitivity Analyses: Mean AUC0-72 of NRS-A Pain Intensity Scores for the Primary and 1st Key Secondary Endpoints

	HTX-011 60 mg/1.8 mg	Saline Placebo	Bupivacaine HCl 50 mg
AUC_{0-72} using LOCF/WOCF in the ITT Population			
n	157	100	155
Mean (SD)	292.93 (165.709)	375.19 (141.521)	348.24 (132.339)
LSMD (SE) [95% CI] vs saline placebo	-82.26 (18.941) [-119.50, -45.03]		
p-value vs saline placebo	<0.0001		
LSMD (SE) [95% CI] vs bupivacaine HCl	-55.31 (16.763) [-88.26, -22.36]		
p-value vs bupivacaine HCl	0.0011		
AUC_{0-72} using wWOCF in the Per Protocol Population			
n	142	83	138
Mean (SD)	311.26 (181.732)	429.98 (155.810)	391.31 (153.983)
LSMD (SE) [95% CI] vs saline placebo	-118.72 (22.908) [-163.77, -73.67]		
p-value vs saline placebo	<0.0001		
LSMD (SE) [95% CI] vs bupivacaine HCl	-80.05 (19.818) [-119.03, -41.08]		
p-value vs bupivacaine HCl	<0.0001		

Abbreviations: AUC_{0-72}, area under the curve from Time 0 through 72 hours; ITT, Intent-to-Treat; LOCF, last observation carried forward; LSMD, least squares mean difference; NRS-A, Numeric Rating Scale of pain intensity score with activity; WOCF, worst observation carried forward; wWOCF, windowed worst observation carried forward.
Notes: Statistics reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect; LSMD is for HTX-011 minus control (saline placebo or bupivacaine HCl) difference. The Per Protocol Population was defined as all subjects in the ITT Population who did not receive a prohibited rescue medication prior to 72 hours and who had no important protocol deviations prior to 72 hours.
Sources: Table 14.2.1.2, Table 14.2.1.3.

The results are in line with those observed for the primary analysis and favour HTX-011 compared to saline placebo and bupivacaine HCl.

The applicant provided additional analysis of mean pain intensity scores over different time intervals during the 72 hours post-dose (AUC of NRS-A).

Table 23: Mean AUC of NRS-A Pain Intensity Scores Over Time Intervals Using wWOCF (ITT Population)

	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=100)	Bupivacaine HCl 50 mg (N=155)
AUC_{0-8}			
Mean (SD)	20.68 (17.536)	37.55 (15.647)	24.26 (14.234)
p-value vs saline placebo	<0.0001		<0.0001
p-value vs bupivacaine HCl	0.0477		
AUC_{0-12}			
Mean (SD)	38.54 (28.076)	67.97 (22.978)	50.37 (22.936)
p-value vs saline placebo	<0.0001		<0.0001
p-value vs bupivacaine HCl	<0.0001		
AUC_{0-24}			
Mean (SD)	98.65 (59.547)	155.75 (48.485)	131.36 (48.861)
p-value vs saline placebo	<0.0001		0.0004
p-value vs bupivacaine HCl	<0.0001		
AUC_{24-48}			
Mean (SD)	119.31 (68.016)	162.07 (60.020)	148.46 (57.119)
p-value vs saline placebo	<0.0001		0.0885
p-value vs bupivacaine HCl	<0.0001		

	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=100)	Bupivacaine HCl 50 mg (N=155)
AUC_{0-48}			
Mean (SD)	217.96 (122.319)	317.82 (102.752)	279.83 (98.428)
p-value vs saline placebo	<0.0001		0.0069
p-value vs bupivacaine HCl	<0.0001		
AUC_{48-72}			
Mean (SD)	105.34 (67.096)	127.52 (61.212)	113.63 (66.208)
p-value vs saline placebo	0.0083		0.0984
p-value vs bupivacaine HCl	0.2634		
AUC_{24-72}			
Mean (SD)	224.64 (131.276)	289.59 (115.642)	262.09 (117.250)
p-value vs saline placebo	<0.0001		0.0806
p-value vs bupivacaine HCl	0.0072		
AUC_{0-72}			
Mean (SD)	323.29 (182.641)	445.34 (155.792)	393.45 (153.756)
p-value vs saline placebo	<0.0001		0.0151
p-value vs bupivacaine HCl	0.0002		

Abbreviations: AUC, area under the curve; ITT, Intent-to-Treat; NRS-A, Numeric Rating Scale of pain intensity score with activity; wWOCF, windowed worst observation carried forward.
Note: P-values reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect.
Sources: Table 14.2.5.1, Post Hoc Table 14.2.3.7, Post Hoc Table 14.2.3.11.

The difference on mean AUC0-72 of the NRS-A pain intensity scores between saline placebo and bupivacaine HCl is statistically significant in favour of the active comparator. According to the applicant, this suggest a confirmation that bupivacaine is active. However, this result was not expected (cf. determination of sample size) and no discussion about it has been found.

The results concerning the comparison between saline placebo and bupivacaine HCl group in the first hours post-dose (AUC0-8 and AUC0-12) suggest, according to the applicant, that most of the analgesic benefit in this group was observed in the first 8 to 12 hours, which is supported by current scientific literature. However, the fact that larger overall intervals (AUC 0-24, AUC0-48 and AUC0-72) are statistically significant in favour of bupivacaine while the intermediate intervals are not (AUC24-48, AUC48-72 and AUC24-72) suggests a limit of the clinical interpretation of the selected endpoint (mean AUC0-72 of NRS-A pain intensity scores).

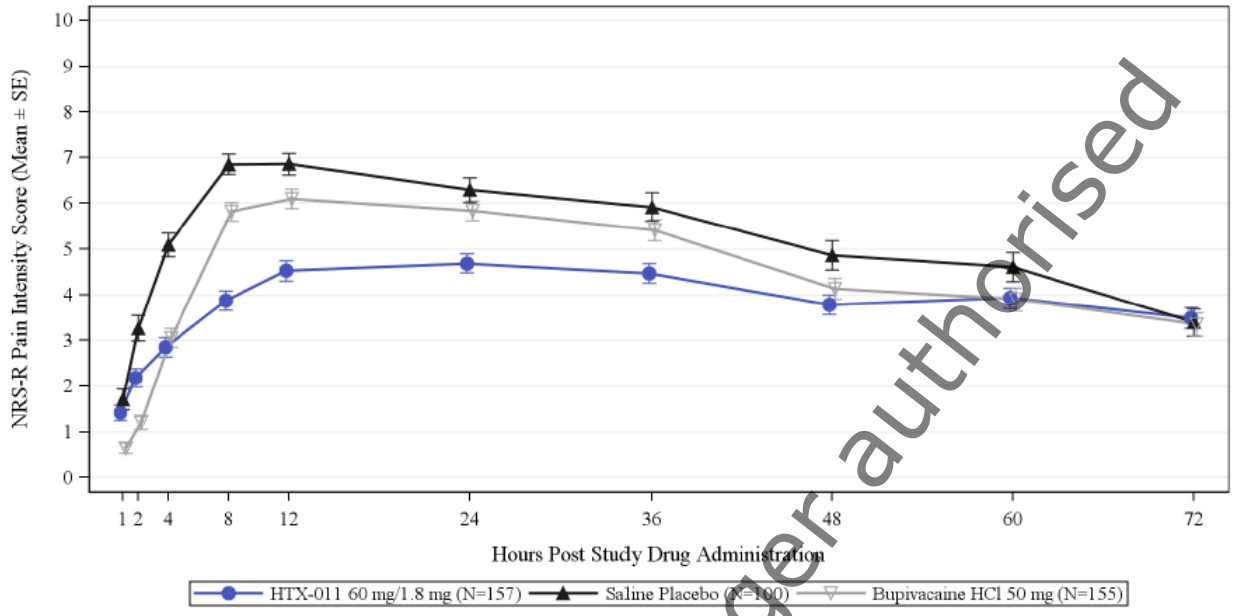
It should be noted that there is no statistically significant difference between HTX-011 and bupivacaine HCl groups from 48 to 72 hours post-dose (AUC48-72). When looking at the respective differences during 72 hours in AUC between placebo and HTX-011 ([AUC 0-72 (PB)] – [AUC 0-72 (ZYN)]), the proportions represented by the first 24 hours ([AUC 0-24 (PB)] – [AUC 0-24 (ZYN)]) are about 50% of the total difference. This is not in contradiction with supposed postoperative pain trajectory, where the first 3 postoperative days is the time period of most severe pain, as mentioned by the applicant, and considering that it has been reported that during these 3 most painful days, the first 24 hours could represent the most painful hours. However, it could not be excluded that the effect size on the overall interval (0-72 hours) may be mainly driven by the effect size on the first day post-dose (0-24 hours).

When looking at the differences in mean pain scores (NRS-A), it seems unquestionable that Zynrelef has a clinically significant effect on reduction of pain scores during the first 24 hours post-dose compared to both saline placebo and bupivacaine HCl. After 24 hours, the differences in pain scores are maintained between 1 and 2 (on a 10 points scale, NRS-A) until 60 hours when HTX-011 is compared to saline placebo. When compared to bupivacaine, the differences in pain scores are maintained between 1 and 2 (on a 10 points scale, NRS-A) until 36 hours. At 48 hours, the difference is close to one (bupivacaine HCl vs HTX-011). At 72 hours, there is no clinically significant difference between treatments.

According to the applicant, the results for NRS-R were consistent with NRS-A. The HTX-011 group had statistically significant reduced mean AUCs of NRS-R pain intensity scores using wWOCF on the ITT population compared with both control groups over the first 24, 48, and 72 hours (AUC0-24, AUC0-48 and AUC0-72). However, there is no statistically significant difference between HTX-011 and both control groups over 48 hours (AUC48-72).

Mean AUCs of NRS-R pain intensity scores over time were analyzed using LOCF/WOCF as sensitivity analyses. Mean AUCs of NRS-R were lower than saline placebo and bupivacaine HCl with statistically significant treatment group differences noted for 0 to 12 hours, 0 to 24 hours, and 0 to 48 hours (AUC0-12, AUC0-24 and AUC0-48). The HTX-011 group also had lower mean AUC of pain intensity score over 72 hours with statistically significant difference compared with saline placebo but not compared with bupivacaine HCl for 0 to 72 hours (AUC0-72). Also, there is no statistically significant difference between HTX-011 and both control groups after 24 hours (AUC24-48 and AUC48-72).

Figure 24: Mean (SE) NRS-R Pain Intensity Scores at Each Assessed Timepoint through 72 Hours Using wWOCF ITT Population



The applicant provided analysis of proportion of subjects with moderate or severe pain intensity:

Table 24: Proportion of subjects with NRS-A ≥4 or ≥7 at any time through 24, 48, and 72 hours (wWOCF, ITT Population)

	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=100)	Bupivacaine HCl 50 mg (N=155)
NRS-A ≥7 at Any Time Through 72 Hours	84 (53.5%)	83 (83.0%)	117 (75.5%)
p-value vs saline placebo	<0.0001		
p-value vs bupivacaine HCl	<0.0001		
NRS-A ≥4 at Any Time Through 72 Hours	136 (86.6%)	97 (97.0%)	148 (95.5%)
p-value vs saline placebo	0.0043		
p-value vs bupivacaine HCl	0.0090		

Abbreviations: ITT, Intent-to-Treat; NRS-A, Numeric Rating Scale of pain intensity score with activity; wWOCF, windowed worst observation carried forward.
Notes: p-values from Fisher's exact test. Exact 95% CI is based on Farrington-Manning score statistics.
Source: Table 14.2.14.

Based on NRS-A, 53.5% of subjects in the HTX-011 group experienced severe pain at any time over 72 hours compared with 83.0% in the saline placebo group and 75.5% in the bupivacaine HCl group. These results are statistically significant. Based on NRS-R, 37.6% of subjects in the HTX-011 group experienced severe pain at any time over 72 hours compared with 73.0% in the saline placebo group and 60.0% in the bupivacaine HCl group. These results are statistically significant.

Overall, a large majority of subjects experienced moderate pain whatever the considered treatment group. This proportion was however lower in the HTX-011 group with statistical significance based on NRS-A (but not based on NRS-R). Considering severe pain, the difference in proportion of subjects is

statistically significant in favor of HTX-011 group but is also numerically significant based on NRS-A and NRS-R. These results suggest that HTX-011 could be an interesting treatment as part of a multimodal approach to manage postoperative pain and to increase probability to avoid severe pain on patients.

Applicant was requested to present proportions of patients with a NRS-A<4 at baseline, 12, 24 and 72 hours for studies 209 – cohort 2, 211, 301 and 302, and to consider these results in the discussion of the clinical relevance of treatment effects.

Regarding study 301, treatment with HTX-011 results in a significant greater the proportion of patients with NRS-A score ≤ 4 at 12 and 24 hours. However, this was not the case at 72 hours. The justification of Applicant is that pain is expected to decrease for this surgery as it is seen in the placebo group with a proportion of about 40% subjects with NRS-A score ≤ 4 at 72 hours. It could then be questioned the rational of using this surgery models to show significant efficacy for 72 hours even though it is expected that curve of pain scores over time have great probability to cross or to be very close at this time point as it is seen in this application for phase 3 studies (301 and 302). Overall, it seems that no firm conclusion can be drawn with these results at 72 hours (proportion of subjects with NRS-A score ≤ 4). The result at 12 and 24 hours are in line with previous results showing efficacy of Zynrelef the first day post-surgery.

Table 25: Incidence of Rescue Medication use through 72 hours (ITT population)

	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=100)	Bupivacaine HCl 50 mg (N=155)
Subjects who received rescue medication			
Any rescue medication	143 (91.1%)	99 (99.0%)	151 (97.4%)
Any opioid rescue medication	112 (71.3%)	98 (98.0%)	138 (89.0%)
Only non-opioid rescue medication	31 (19.7%)	1 (1.0%)	13 (8.4%)
Use of rescue medication by generic name			
Opioid rescue medications			
Oxycodone/oxycodone hydrochloride[a]	112 (71.3%)	98 (98.0%)	138 (89.0%)
Morphine/morphine sulfate[b]	42 (26.8%)	54 (54.0%)	68 (43.9%)
Non-opioid rescue medications			
Paracetamol	122 (77.7%)	85 (85.0%)	127 (81.9%)

Abbreviation: ITT, Intent-to-Treat.
Notes: Medications were coded to generic drug names using the World Health Organization Drug Dictionary Enhanced (WHODDE), Version 01 September 2016. At each level of summarization (any medication, generic drug name), subjects reporting use of more than one medication were counted only once.
[a] Subjects taking oxycodone and/or oxycodone hydrochloride were pooled.
[b] Subjects taking morphine and/or morphine sulfate were pooled.
Sources: Table 14.1.8.4, Table 14.1.8.2, Post Hoc Table 14.1.8.6.

These results on incidence of rescue medication confirm the need of a multimodal approach to manage postoperative pain as supported by scientific literature. More than 90% of subjects needed rescue medication whatever the considered treatment group.

The proportion of subjects who received any opioid rescue medication through 72 hours is reduce in HTX-011 group (71.3%) compared to saline placebo (98%) and bupivacaine HCl groups (89%).

It should be noted that substantially more subjects used only non-opioid rescue medication (paracetamol) in the HTX-011 group. It may express, as suggested by Applicant, that subjects could managed their pain only with paracetamol (acetaminophen).

The median time to the first use of opioid rescue medication during the 72-hour postoperative period was statistically significantly longer in the HTX-011 group compared with saline placebo and bupivacaine HCl (12.18 hours vs 4.90 and 7.60 hours, respectively).

As requested, the applicant provided an analysis of time to first rescue medication (opioid and paracetamol). Overall, HTX-011 delayed the time to first use of opioid rescue medication and increased the proportion of subjects who did not require opioid rescue medication. However, as previously mentioned, the applicant explained that surgery was performed under regional anaesthesia with a lidocaine Mayo block, which provides several hours of analgesia. The low pain scores across groups following a Mayo block in this study likely led to smaller differences between HTX-011 and saline placebo at 2 and 4 hours.

Table 26: Proportion of Subjects who are Opioid-Free through Day 10 or through Day 28 (ITT Population)

	HTX-011 60 mg/1.8 mg	Saline Placebo	Bupivacaine HCl 50 mg
All subjects	N=157	N=100	N=155
Opioid-free through Day 10	**41 (26.1%)**	**2 (2.0%)**	**15 (9.7%)**
Difference (95% CI) vs saline placebo	24.1% (16.0%, 32.0%)		
p-value vs saline placebo	<0.0001		
Difference (95% CI) vs bupivacaine HCl	16.4% (7.4%, 25.1%)		
p-value vs bupivacaine HCl	0.0002		
Opioid-free through Day 28	**37 (23.6%)**	**2 (2.0%)**	**14 (9.0%)**
Difference (95% CI) vs saline placebo	21.6% (13.8%, 29.3%)		
p-value vs saline placebo	<0.0001		
Difference (95% CI) vs bupivacaine HCl	14.5% (5.9%, 22.9%)		
p-value vs bupivacaine HCl	0.0007		
Subjects who are opioid-free through 72 hours	n=45	n=2	n=17
Remained opioid-free through Day 10	41/45 (91.1%)	2/2 (100.0%)	15/17 (88.2%)
Remained opioid-free through Day 28	37/45 (82.2%)	2/2 (100.0%)	14/17 (82.4%)

Abbreviation: ITT, Intent-to-Treat.
Notes: Opioid-free through 72 hours is defined as having total morphine milligram equivalent (MME) opioid dose = 0 during the 72-hour on-site postoperative period, based on concomitant medication data. Opioid-free through Day 10 is defined as MME = 0 through 72 hours and answering "No" to the diary question "Did you take any opioid medication?" every day from 72 hours through Day 10. Opioid-free through Day 28 is defined similarly. Subjects who answered "Yes" or had a missing answer on any day during the period, or withdrew from the study during the period, were not considered opioid-free. A total of 64 subjects from 2 sites did not receive a diary upon discharge; concomitant medication data was used for these 64 subjects for opioid-free analyses through Day 10 and Day 28. 95% CIs are based on Farrington-Manning score statistics. P-values from Fisher's exact test.
Sources: Post Hoc Table 14.2.3.5, Post Hoc Table 14.2.3.6.

Provided results suggest an opioid sparing effect maintained over time for a sub-group of subjects as a large majority of opioid-free subjects during the 72 hours post-dose period, where most severe postoperative pain occurs, do not need opioid to control pain at Day 10 and Day 28 post-dose. However, the number of patients who lost the analgesic effect during the period from 72 hours up to Day 10 and Day 28 was higher in HTX-011, what may indicate that HTX-011 is not superior to Bupivacaine HCl in maintenance of opioid-free status over the time. The applicant was requested to discuss this point. The applicant provided re-analysis on the opioid-free status of participants in Study 301 and Study 302, taking into account major findings during inspection, which revealed a systematic problem regarding

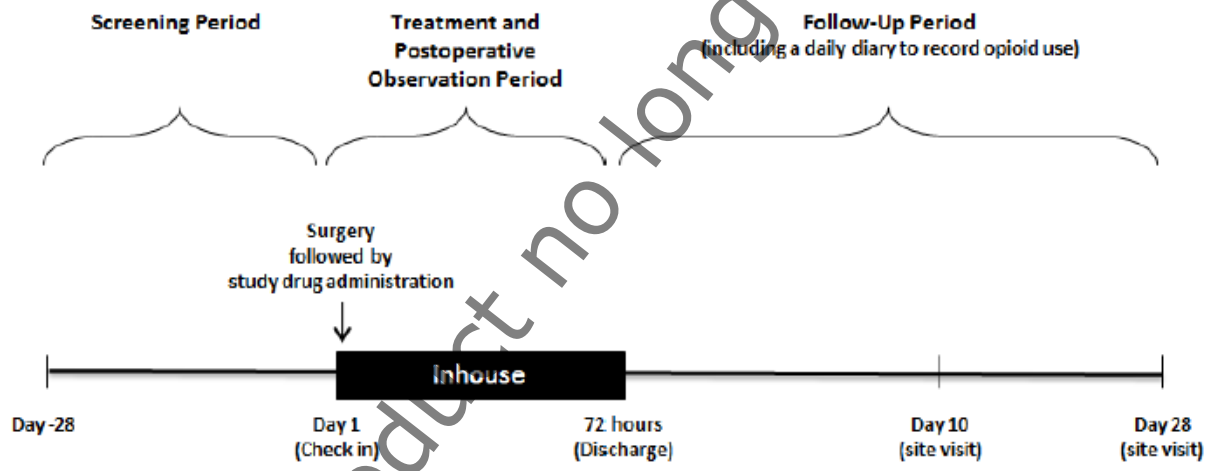
errors in use of opioid diaries. There were numerous discrepancies between the post discharge opioid use data in patient diaries and data reported in the CSR. The results of re-analysis showed that proportion of subjects who were opioid-free and remained opioid-free through Day 10 was similar and through Day 28 was higher than in Bupivacaine HCl arm. Mean NRS-A Pain Scores at the Day 10 and Day 28 was lower in HTX-011 arm.

A Phase 3, Randomized, Double-Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Local Administration for Postoperative Analgesia and Decreased Opioid Use Following Unilateral Open Inguinal Herniorrhaphy

Methods

The study consisted in the following phases:

Figure 25



The study design is similar to study 301 in bunionectomy. Inguinal herniorrhaphy is not a surgical model cited in the Guideline on the clinical development of medicinal products intended for the treatment of pain but it is one of the most common soft tissue procedures performed in clinical practice. Acute pain after inguinal herniorrhaphy could be considered as generally moderate. Development of chronic pain after inguinal herniorrhaphy is highlighted in the scientific literature as the major complication of this surgical procedure with an estimated incidence of 10%. Postoperative pain is considered chronic if it persists more than 3 months after the intervention. Poor management of acute postoperative pain may be a risk factor of developing chronic pain as intensity of acute postoperative pain has been reported to correlates with the risk of developing a persistent pain. Thus, it would have been interesting to extend the follow up and to check for persistent pain across the different treatment groups.

Study Participants

Main inclusion criteria

Each subject had to meet all of the following criteria to be enrolled in this study:

1. Was male or female, and ≥18 years of age at screening.

2. Was scheduled to undergo a unilateral open inguinal herniorrhaphy with mesh under general anesthesia.

3. Had an American Society of Anesthesiologists Physical Status of I, II, or III

Main exclusion criteria

Subjects who met any of the following criteria were not to be enrolled in the study:

1. Had any prior inguinal hernia repair except as a child (less than 6 years of age).

2. Had a planned concurrent surgical procedure (eg, bilateral herniorrhaphy).

3. Had a pre-existing concurrent acute or chronic painful physical/restrictive condition expected to require analgesic treatment in the postoperative period for pain that was not strictly related to the herniorrhaphy and which may confound the postoperative assessments.

4. Had a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction to bupivacaine (or other local anesthetics), meloxicam (or other NSAIDs), oxycodone, morphine, acetaminophen/paracetamol, or fentanyl.

5. Had known or suspected daily use of opioids for 7 or more consecutive days within the previous 6 months.

6. Had taken NSAIDs (including meloxicam) within 10 days prior to the scheduled surgery with the exception of subjects on low dose (≤100 mg) daily acetylsalicylic acid for cardioprotection.

7. Had taken long-acting opioids within 3 days prior to the scheduled surgery.

8. Had taken any opioids within 24 hours prior to the scheduled surgery.

9. Had been administered bupivacaine within 5 days prior to the scheduled surgery.

10. Had been administered any local anesthetic within 72 hours prior to the scheduled surgery, other than for pretreatment prior to a needle placement, to treat an AE that occurs after signing the ICF, or to decrease venous irritation (eg, caused by propofol, in which case no more than a single administration of lidocaine 1% 20 mg IV could be administered).

Treatments

The study population was randomized into three treatment groups in a 2:2:1 pattern generated by computer as follows:

- HTX-011, bupivacaine 300 mg / meloxicam 9 mg (10.3 mL) via instillation into the surgical site using a Luer lock applicator.
- Bupivacaine HCl without epinephrine 0.25%, 75 mg (30 mL), via injection into the surgical site.
- Saline placebo, 0.9% sodium chloride (10.3 mL) via instillation into the surgical site using a Luer lock applicator.

The surgical procedure was performed under general anesthesia. During surgery, the use of IV fentanyl up to 4 µg/kg was permitted for intraoperative pain control. Just prior to the end of the surgery, all subjects received an additional 50 µg IV fentanyl in order to decrease the inherent variability of intraoperative pain control on immediate postoperative pain.

Rescue medication

Postoperative rescue medication consisted of (PO) immediate-release oxycodone (no more than 10 mg within a 4-hour period as needed), IV morphine (no more than 10 mg within a 2-hour period as needed), and/or oral acetaminophen (no more than 1,000 mg in a 6-hour period). Rescue medication was administrated upon request.

At discharge, subjects were to be provided a daily diary to record if they took any opioid medication from 72 hours through Day 28 (yes or no).

Procedure regarding instillation of HTX-011 and bupivacaine injection were standardized and well described.

The dose of bupivacaine HCl used in this study is within the range of dosing in bupivacaine labeling provided and, according to the applicant, was based on advice from medical experts who stated that doses commonly used in herniorrhaphy range from approximately 20 to 30 mL using a 0.25% solution. The dose selected for this study, 30 mL of 0.25% solution (75 mg), reflected the maximum dose and maximum concentration recommended. This seems acceptable. However, as a single-dose is used for postoperative pain management in this study, the selection of bupivacaine dose is crucial and it is considered this point should be further justified.

Objectives

Primary objective:

To compare the efficacy and duration of analgesia following local administration of HTX-011 with saline placebo during the first 72 hours following unilateral open inguinal herniorrhaphy.

Secondary objectives:

- To compare the efficacy and duration of analgesia for HTX-011 with bupivacaine HCl without epinephrine during the first 72 hours following surgery.
- To compare the effect of HTX-011 with saline placebo and bupivacaine HCl without epinephrine on opioid load during the first 72 hours following surgery.
- To assess the safety and tolerability of HTX-011.
- To further establish the PK parameters of bupivacaine and meloxicam in HTX-011.

The objectives of this study are identical to those of study 301 in bunionectomy and are appropriate.

Outcomes/endpoints

Primary Endpoint

Mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) through 72 hours (AUC0-72) for HTX-011 compared with saline placebo.

Key secondary endpoints

- Mean AUC0-72 of the NRS-A pain intensity scores for HTX-011 compared with bupivacaine HCl.
- Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with saline placebo.

- Proportion of subjects who are opioid-free through 72 hours for HTX-011 compared with bupivacaine HCl.
- Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with bupivacaine HCl.

Other secondary efficacy endpoints

- Proportion of subjects who are opioid-free through 72 hours compared with saline placebo.
- Proportion of subjects who are opioid-free from 72 hours through Day 10 and Day 28.
- Median time in hours to first opioid rescue medication up to 72 hours.
- Mean AUC0-72 of the NRS-R pain intensity scores.
- Integrated Rank Analysis of Silverman using the NRS-A pain intensity AUC scores and total opioid consumption through 72 hours.
- Proportion of subjects who are pain-free with activity (defined as an NRS-A pain intensity score of 0 or 1) at each assessed timepoint through Day 28.
- Proportion of subjects with an NRS-A pain intensity score ≥4 at any timepoint through 72 hours.
- Proportion of subjects with an NRS-A pain intensity score ≥7 at any timepoint through 72 hours.
- Proportion of subjects who first achieve an MPADSS score ≥9 at 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours.
- Proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA at 24, 48, 72 hours, and on Day 28.

Pain intensity assessments

Subjects were asked to evaluate their current pain level at scheduled timepoints after surgery. Pain intensity scores were assessed using an 11-point NRS (0–10) where 0 represented "no pain" and 10 represented "worst pain imaginable" (Breivik 2008). NRS scores were recorded first at rest (NRS-R) and then with activity (NRS-A).

For NRS-R assessments, subjects were subjects were recumbent or lying supine. Measurements were obtained after the subject was in the resting position for at least 5 minutes.

For NRS-A assessments, subjects were recumbent or lying supine and were instructed to sit up. Measurements were obtained as soon as the subject sat up from the resting position.

Pain intensity assessments were scheduled at 1, 2, 4, 8, 12, 24, 36, 48, 60, 72 hours and at D10 and D28 post-dose.

Discharge readiness

Discharge readiness was assessed using the MPADSS criteria (Chung 1995). This study instrument was used to assess each subject's potential readiness to be discharged and was repeated at all scheduled timepoints (2, 4, 8, 12, 24, 36, 48, 60 and 72 hours post-dose). It was not intended to be used to decide whether or not to discharge a subject from the hospital/research facility. Subjects were required to remain in the hospital/research facility for 72 hours.

Patient global assessment of pain control

Subjects were asked to evaluate their pain control over the preceding 24 hours using a 4-point PGA scale where 0 represented "poor" and 3 represented "excellent" (Rothman 2009).

Scheduled timepoints were: 24, 48, 72 hours and D28 post-dose.

Efficacy endpoints are identical to those of pivotal study 301 in bunionectomy. The prescribed activity for NRS-A in subjects undergoing herniorrhaphy was sitting up from a resting position. This is acceptable.

Sample size

Sample size was determined by the applicant based on the estimate of the following parameters from a previous phase 2 study in subjects undergoing unilateral open inguinal herniorrhaphy:

Table 27

Parameter	Saline Placebo	Bupivacaine HCl	HTX-011 300 mg/9 mg
Pain intensity AUC_{0-72}: Mean (SD)	400 (150)	350 (150)	275 (200)
Opioid consumption (mg): Mean (SD)	30 (25)	23 (25)	12 (25)
Proportion of opioid-free subjects	10%	20%	40%

Approximately 400 subjects (160 subjects in the HTX-011 group, 160 subjects in the bupivacaine HCl active control group, and 80 subjects in the saline placebo control group) were planned to be randomized to provide at least 90% power to detect a statistically significant difference (2-sided alpha=0.05) between the HTX-011 group and each of the control groups for each of the primary and key secondary endpoints.

Studies appear sufficiently powered according to the criteria selected. The clinical relevance of the expected difference in terms of AUC0-72 of the pain intensity score between HTX-011 and bupivacaine HCl/placebo has not been justified.

Randomisation and blinding (masking)

study population was randomized into three treatment groups in a 2:2:1 pattern. The site's pharmacy and surgical staff were not blinded to the treatment assignments because HTX-011 is a colored, viscous substance and is therefore distinguishable from both bupivacaine HCl and saline placebo. However, subjects were not aware of the study drug they received, and once surgery was completed and the subject was transferred to the PACU, the Investigator and all site staff involved in safety and efficacy assessments were blinded to the treatment assignment until after database lock. The study blind at the site was not to be broken except in medical emergencies when the appropriate management of the subject required knowledge of the study drug he/she received.

Statistical methods

Analysis populations

- Intent-to-Treat (ITT) Population: All subjects who were randomized and received study drug were included in the ITT Population.
- Per Protocol Population: All subjects in the ITT Population who did not receive a prohibited rescue medication prior to 72 hours and who had no important protocol violations prior to 72 hours were included in the Per Protocol Population.
- Safety Population: All subjects who received study drug were included in the Safety Population.

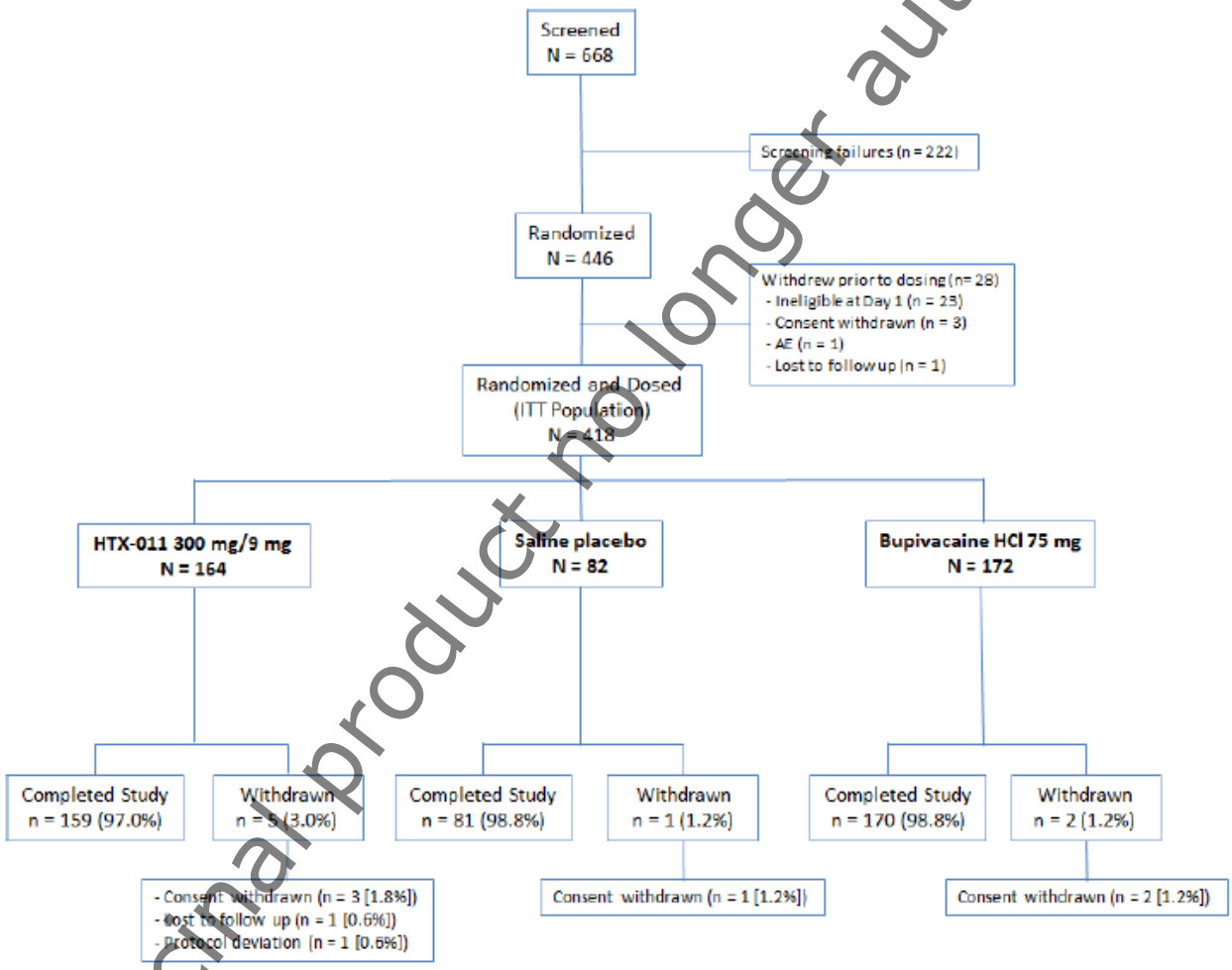
Overall the statistical methods is identical to study 301 in bunionectomy and seems acceptable. A hierarchically procedure, in a pre-specified order, has been set to handle multiple comparison in primary and key secondary endpoints.

The definitions of ITT, PP and safety populations are appropriate.

Windowed worst observation carried forward (wWOCF) was used to adjust the NRS-A through 72 hours scores for the duration effect of opioid rescue medications. However, wWOCF was not used to adjust scores for the duration of effect of non-opiod recue medications (acetaminophen).

Results

Figure 26: Participant flow



Abbreviations: AE, adverse event; ITT, Intent-to Treat.
Notes: Screened was defined as signing an informed consent form. Completed the study was defined as completing the Day 28 Visit. One subject randomized to the HTX-011 group was misdosed; the subject received bupivacaine HCl instead of HTX-011.
Source: Table 14.1.1.1.

Baseline data

The overall study population was predominantly male (94.5%). The mean (SD) age was 48.9 (12.75) years, ranging from 18 to 83 years, and the mean BMI (SD) was 27.21 (4.058) kg/m2. The study subjects were overall well balanced across treatment's groups. Inguinal hernia is a common pathology

affecting mainly men. It could exist from birth (congenital) and be for example revealed during an effort in the young adult. In the older subject, it results more from a progressive weakness of the muscles and fibrous tissues of the lower abdomen. Regarding median age and sex ratio, it is considered that study population is adequate.

Numbers analysed

Table 28: Number of Subjects per Analysis Population

Analysis Populations	HTX-011 300 mg/9 mg	Saline Placebo	Bupivacaine HCl 75 mg	Total
Randomized	178	89	179	446
ITT	164	82	172	418
Safety	163[a]	82	173[a]	418
Per Protocol	145	71	148	364

Abbreviations: ITT, Intent-to-Treat.
Notes: The ITT Population included all subjects who were randomized and received study drug. The randomized treatment assignment was used for analysis the ITT Population. The Safety Population included all subjects who received study drug. The actual treatment received was used for analysis in the Safety Population. The Per Protocol Population included all subjects in the ITT Population who did not receive a prohibited rescue medication prior to 72 hours and who had no important protocol deviations prior to 72 hours.
[a] One subject was randomized to HTX-011, but received bupivacaine HCl.
Source: Table 14.1.1.1.

Outcomes and estimation

Primary endpoint and first key secondary endpoint: Mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) through 72 hours (AUC0-72)

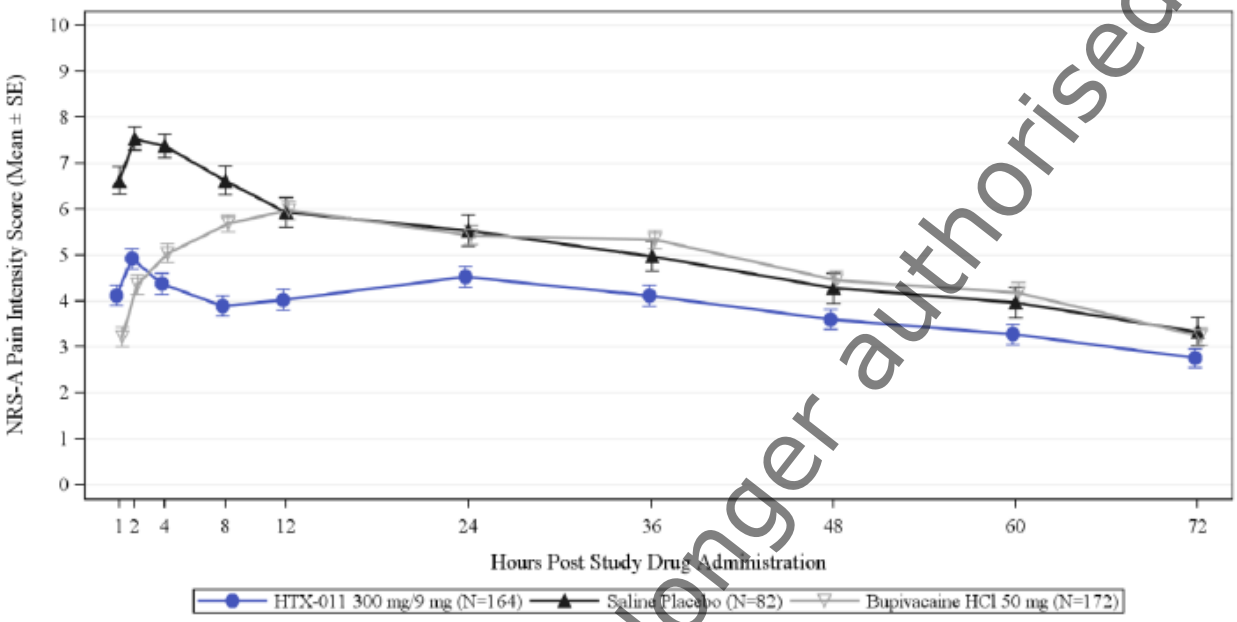
Table 29: Mean AUC0-72 of the NRS-A Pain Intensity Scores for HTX-011 vs Saline Placebo and Bupivacaine HCl (wWOCF, ITT Population)

	HTX-011 300 mg/9 mg (N=164)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=172)
AUC_{0-72}			
Mean (SD)	269.39 (173.719)	350.82 (171.224)	341.88 (158.303)
LSMD (SE) [95% CI] vs saline placebo	-81.43 (22.592) [-125.83, -37.02]		
p-value vs saline placebo	0.0004		
LSMD (SE) [95% CI] vs bupivacaine HCl	-72.49 (18.230) [-108.32, -36.65]		
p-value vs bupivacaine HCl	<0.0001		

Abbreviations: AUC_{0-72}, area under the curve from Time 0 through 72 hours; ITT, Intent-to-Treat; LSMD, least squares mean difference; NRS-A, Numeric Rating Scale of pain intensity score with activity; wWOCF, windowed worst observation carried forward.
Note: p-values reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect.
Source: Table 14.2.1.1.

The mean AUC0-72 of the NRS-A pain intensity score was lower in the HTX-011 group compared with saline placebo (primary endpoint) and compared with bupivacaine HCl (first key secondary endpoint) and the differences are statistically significant.

Figure 27: Mean NRS-A Pain Intensity Scores over time (wWOCF, ITT Population)



Abbreviations: ITT, Intent-to-Treat; NRS-A, Numeric Rating Scale of pain intensity score with activity; wWOCF, windowed worst observation carried forward.
Source: Figure 14.2.7.

With the exception of the first 2 hours after study drug administration, where mean NRS-A pain intensity scores is lower in the bupivacaine group, HTX-011 presents lower NRS-A pain intensity scores compared with saline placebo and bupivacaine groups through 72 hours.

It is difficult to appreciate the clinical relevance of these differences. The clinically relevant difference for comparing the mean AUC0-72h of pain intensities has not been initially discussed or justified. As a consequence, clinical translation of obtained results in AUC are difficult to extrapolate and are open to interpretation. The applicant proposed a justification of the clinical significance based on a 10% to 20% reduction in NRS pain intensity scores as a minimal clinically important difference (MCID) defined by The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) in chronic pain that is not considered fully adapted.

Graphically, the most important differences in pain scores between HTX-011 and both of the control groups occurred during the first 24 hours. Between 24 and 72 hours post-dose, the curves of pain scores corresponding to placebo, bupivacaine HCl and HTX-011 are practically parallel. The difference in pain scores between groups is close to 1/10. Overall, this may suggest a spontaneous reduction of pain 24 hours after surgery. HTX-011 effect on pain after 24 hours does not appear clearly.

Second and fourth key secondary endpoints: Mean total postoperative opioid consumption (in iv morphine equivalents) through 72 hours

Table 30: Total Postoperative Opioid Consumption (MME) through 72 hours for HTX-011 vs Saline Placebo and Bupivacaine HCl (ITT Population)

	HTX-011 300 mg/9 mg (N=164)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=172)
Total Postoperative Opioid Consumption Through 72 Hours			
Mean (SD)	10.85 (17.062)	17.53 (18.908)	14.51 (18.185)
Median (Min, Max)	0.00 (0.0, 103.0)	11.25 (0.0, 73.5)	7.25 (0.0, 87.5)
p-value vs saline placebo	0.0001		
p-value vs bupivacaine HCl	0.0240		

Abbreviations: ITT, Intent-to-Treat; MME, morphine milligram equivalent.
Note: Opioid rescue medication included morphine, oxycodone, fentanyl, and hydrocodone. P-values were obtained using the Wilcoxon rank sum test.
Source: Table 14.2.2.1.

These results show an overall lower consumption of opioids in HTX-011 group compared with saline placebo and bupivacaine HCl groups. However, the intragroup differences between the minimal and the maximal consumption are high and similar between treatment groups. Numerically, the mean and median differences between the groups, in particular between HTX-011 and bupivacaine HCl groups, seem modest. In HTX-011 group, over 72 hours, mean total opioid consumption is reduced by 38% compared with saline placebo and by 25% compared with bupivacaine HCl. As requested, the applicant justified the clinical significance of the opioid sparing effect in particular for outcomes in patients, with an overall reduction of prespecified ORAEs with HTX-011 compared to saline placebo and bupivacaine: 32.5% vs 43.9% vs 42.2% respectively.

It is endorsed that HTX-011 allowed an opioid sparing effect of about 6 to 7 of morphine mg equivalent in the first 24 hours compared to placebo which is under what seems to be possibly achieved with other analgesics such as paracetamol and NSAIDs. These 6 to 7 morphine mg equivalent sparing achieved in the first 24 hours is the most important sparing effect achieved on the overall interval of 72 hours (about 50% of the total opioid sparing). It could be hypothesized that the opioid sparing effect on the overall interval (0-72 hours) may be mainly driven by the opioid sparing effect on the first day post-dose (0-24 hours). Overall, the applicant successfully justified an opioid sparing effect associated with a decrease in ORAE. The estimation of the effect size is limited by the study design. Indeed, patient controlled analgesia (PCA) appears to be the method of choice to estimate opioid sparing effect because an accurate measure of postoperative opioids needs should be preferably based on a method where patients can "freely" access to opioids to relieve pain and accept some degree of undesirable effects. In addition, to a lesser extent, effect is limited by the use of paracetamol but its influence on opioid sparing is considered limited because the proportion of subjects who used paracetamol was overall lower in the HTX-011 group ad mean total use of paracetamol and average daily use were similar or lower in HTX-011 compared to the two other groups. This opioid sparing effect of HTX-011 is considered as modest but clinically significant.

Third key secondary and other endpoint: proportion of subjects who are opioid-free through 72 hours

Table 31: Proportion of Subjects Who are Opioid-Free through 72 Hours for HTX-011 vs Saline Placebo and Bupivacaine HCl (ITT Population)

	HTX-011 300 mg/9 mg (N=164)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=172)
Subjects Who Are Opioid-Free Through 72 Hours	84 (51.2%)	18 (22.0%)	69 (40.1%)
Difference (95% CI) vs saline placebo	29.3% (15.6%, 40.5%)		
p-value vs saline placebo	<0.0001		
Difference (95% CI) vs bupivacaine HCl	11.1% (0.3%, 21.8%)		
p-value vs bupivacaine HCl	0.0486		

Abbreviation: ITT, Intent-to-Treat.
Notes: Opioid-free through 72 hours was defined as subjects who had total MME opioid dose of 0 through 72 hours. P-values were derived using Fisher's exact test. Exact 95% CI was based on Farrington-Manning score statistics.
Source: Table 14.2.3.1.

These results show a largely higher proportion of opioid-free subjects over 72 hours post-dose in HTX-011 group compared to saline placebo. When compared to bupivacaine, the proportion of opioid-free subjects over 72 hours is higher in the HTX-011 group and the difference is at the limit of the statistical significance (p=0.0486).

Sensitivity analyses

The applicant proposes sensitivity analyses performed on the primary and first key secondary endpoints to support the robustness of the primary analyses. Results of mean AUC0-72 of NRS-A pain intensity scores are presented without adjusting for opioid use and also using adjustment for opioid use in the per protocol population.

Table 32: Sensitivity Analyses: Mean AUC0-72 of NRS-A Pain Intensity Scores for the Primary and first Key Secondary Endpoints

	HTX-011 300 mg/9 mg	Saline Placebo	Bupivacaine HCl 75 mg
AUC_{0-72} using LOCF/WOCF in the ITT Population			
n	164	82	172
Mean (SD)	244.42 (150.832)	295.86 (136.498)	309.63 (138.433)
LSMD (SE) [95% CI] vs saline placebo	-51.44 (19.350) [-89.47, -13.40]		
p-value vs saline placebo	0.0082		
LSMD (SE) [95% CI] vs bupivacaine HCl	-65.20 (15.614) [-95.89, -34.51]		
p-value vs bupivacaine HCl	<0.0001		

	HTX-011 300 mg/9 mg	Saline Placebo	Bupivacaine HCl 75 mg
AUC_{0-72} using wWOCF in the Per Protocol Population			
n	145	71	148
Mean (SD)	269.57 (176.295)	331.60 (169.568)	335.05 (156.354)
LSMD (SE) [95% CI] vs saline placebo	-62.04 (24.206) [-109.64, -14.43]		
p-value vs saline placebo	0.0108		
LSMD (SE) [95% CI] vs bupivacaine HCl	-65.49 (19.727) [-103.89, -27.09]		
p-value vs bupivacaine HCl	0.0009		

Abbreviations: AUC_{0-72}, area under the curve from Time 0 through 72 hours; ITT, Intent-to-Treat; LOCF, last observation carried forward; LSMD, least squares mean difference; NRS-A, Numeric Rating Scale of pain intensity score with activity; WOCF, worst observation carried forward; wWOCF, windowed worst observation carried forward.
Notes: Statistics reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect; LSMD is for HTX-011 minus control (saline placebo or bupivacaine HCl) difference. The Per Protocol Population was defined as all subjects in the ITT Population who did not receive a prohibited rescue medication prior to 72 hours and who had no important protocol deviations prior to 72 hours.
Sources: Table 14.2.1.2, Table 14.2.1.3.

The results point in the same direction than the primary analysis and favour HTX-011 compared to saline placebo and bupivacaine HCl.

It should however be noted that the mean AUC0-72 of NRS-A pain intensity score is higher in the bupivacaine HCl group compared to the saline placebo group in both sensitivity analyses (without wWOCF in the ITT population and with wWOCF in the per protocol population). This was not the case in the primary analysis even though the mean AUC0-72 of NRS-A pain intensity score were numerically close. This suggest that there is no difference between bupivacaine HCl and placebo in this surgical model.

According to the applicant, sensitivity analyses using the Per Protocol Population on the 2nd, 3rd, and 4th key secondary endpoints were also consistent with the primary analyses. The HTX-011 group had lower total opioid consumption and more opioid-free subjects over 72 hours group compared with saline placebo and bupivacaine HCl.

The applicant provided additional analysis of mean pain intensity scores over different time intervals during the 72 hours post-dose (AUC of NRS-A).

Table 33: Mean AUC of NRS-A Pain Intensity Scores over time Intervals Using wWOCF (ITT Population)

	HTX-011 300 mg/9 mg (N=164)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=172)
AUC_{0-8}			
Mean (SD)	30.58 (18.874)	50.02 (15.033)	34.38 (16.314)
p-value vs saline placebo	<0.0001		<0.0001
p-value vs bupivacaine HCl	0.0426		
AUC_{0-12}			
Mean (SD)	46.31 (29.308)	75.32 (24.590)	57.72 (24.876)
p-value vs saline placebo	<0.0001		<0.0001
p-value vs bupivacaine HCl	0.0001		
AUC_{0-24}			
Mean (SD)	97.72 (60.308)	143.76 (54.942)	126.65 (52.681)
p-value vs saline placebo	<0.0001		0.0238
p-value vs bupivacaine HCl	<0.0001		
AUC_{24-48}			
Mean (SD)	97.79 (64.540)	117.77 (64.116)	122.54 (57.480)
p-value vs saline placebo	0.0170		0.5646
p-value vs bupivacaine HCl	0.0003		
AUC_{0-48}			
Mean (SD)	195.51 (120.382)	261.53 (114.993)	249.19 (106.166)
p-value vs saline placebo	<0.0001		0.4187
p-value vs bupivacaine HCl	<0.0001		
AUC_{48-72}			
Mean (SD)	73.88 (60.573)	89.29 (63.522)	92.69 (58.219)
p-value vs saline placebo	0.0593		0.6737
p-value vs bupivacaine HCl	0.0044		
AUC_{24-72}			
Mean (SD)	171.68 (120.402)	207.05 (122.316)	215.23 (111.973)
p-value vs saline placebo	0.0264		0.6041
p-value vs bupivacaine HCl	0.0007		
AUC_{0-72}			
Mean (SD)	269.39 (173.719)	350.82 (171.224)	341.88 (158.303)
p-value vs saline placebo	0.0004		0.6902
p-value vs bupivacaine HCl	<0.0001		

Abbreviations: AUC, area under the curve; ITT, Intent-to-Treat; NRS-A, Numeric Rating Scale of pain intensity score with activity; wWOCF, windowed worst observation carried forward.
Note: P-values reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect.
Sources: Table 14.2.5.1, Post Hoc Table 14.2.3.7, Post Hoc Table 14.2.3.11.

The difference during the first 8 hours (AUC0-8) in favour of HTX-011 compared with bupivacaine HCl is on the border of statistical significance (p=0.0426).

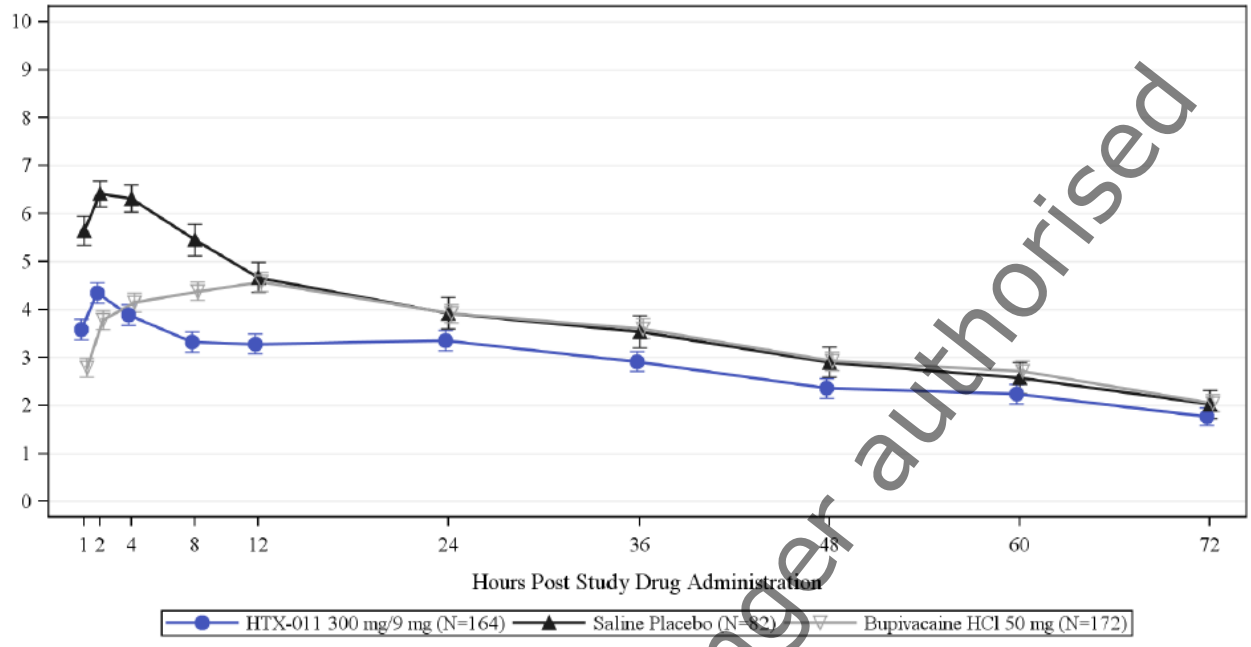
It should be noted that HTX-011 did not result in statistically significant decrease of AUC of pain intensity scores from 48 hours to 72 hours compared to both saline placebo and bupivacaine HCl (AUC 48-72). When looking at the respective differences during 72 hours in AUC between placebo and HTX-011 ([AUC 0-72 (PB)] – [AUC 0-72 (ZYN)]), the proportions represented by the first 24 hours ([AUC 0-24 (PB)] – [AUC 0-24 (ZYN)]) are about 50%. This is not in contradiction with supposed postoperative pain trajectory, where the first 3 postoperative days is the time period of most severe pain, as mentioned by the applicant, and considering that it has been reported that during these 3 most painful days, the first 24 hours could represent the most painful hours. However, it could not be excluded that the effect size on the overall interval (0-72 hours) may be mainly driven by the effect size on the first day post-dose (0-24 hours).

When looking at the differences in mean pain scores (NRS-A), it seems unquestionable that Zynrelef has a clinically significant effect on reduction of pain scores during the first 24 hours post-dose compared to both saline placebo and bupivacaine HCl. However, after 24 hours, the differences in pain scores between saline placebo and HTX-011 are systematically under 1 (on a 10 points scale, NRS-A). The correlation between decrease in AUC and decrease in pain is not straightforward and the minimal decrease in AUC of pain scores that would translate to a minimal decrease in pain that would been considered as clinically significant is not defined. It could be then considered that Zynrelef effect after 24 hours in open inguinal herniorrhaphy is not clinically significant in this study.

According to the applicant, the results for NRS-R were consistent with NRS-A. The HTX-011 group had statistically significant reduced mean AUCs of NRS-R pain intensity scores using wWOCF on the ITT population compared with both control groups over the first 24, 48, and 72 hours (AUC0-24, AUC0-48 and AUC0-72). However, there is no statistically significant difference between HTX-011 and both control groups over 48 hours (AUC48-72).

Mean AUCs of NRS-A and NRS-R pain intensity scores over time were analyzed using LOCF/WOCF as sensitivity analyses. According to the applicant, results were consistent with the primary analyses and although a statistically significant treatment group difference in the AUC of NRS-R pain intensity scores was not achieved for HTX-011 compared with saline placebo for every time period, this is likely due to the smaller sample size of the saline placebo group. It should however be noted that there was no statistically significant difference between HTX-011 and both control groups after 24 hours (AUC24-48 and AUC48-72) and on the overall interval (AUC0-72).

Figure 28: Mean (SE) NRS-R Pain Intensity Scores at Each Assessed Timepoint through 72 Hours Using wWOCF ITT Population



Regarding mean AUCs of NRS-R pain intensity scores over time analyzed using LOCF/WOCF, mean AUCs of NRS-R were lower for HTX-011 compared to saline placebo and bupivacaine HCl with statistically significant treatment group differences noted for 0 to 12 hours, 0 to 24 hours, and 0 to 48 hours (AUC0-12, AUC0-24 and AUC0-48). However, there is no statistically significant difference between HTX-011 and both control groups after 24 hours (AUC24-48 and AUC48-72). There is also no statistically significant difference between HTX-011 and both control groups on the overall interval (AUC0-72).

The applicant provided analysis of proportion of subjects with moderate or severe pain intensity.

Table 34: Proportion of Subjects with NRS-A ≥4 or ≥7 at Any Time through 24, 48, and 72 Hours (wWOCF, ITT Population)

	HTX-011 300 mg/9 mg (N=164)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=172)
NRS-A ≥7 at Any Time Through 72 Hours	**80 (48.8%)**	**67 (81.7%)**	**104 (60.5%)**
p-value vs saline placebo	<0.0001		
p-value vs bupivacaine HCl	0.0372		
NRS-A ≥4 at Any Time Through 72 Hours	**137 (83.5%)**	**81 (98.8%)**	**161 (93.6%)**
p-value vs saline placebo	0.0002		
p-value vs bupivacaine HCl	0.0053		

Abbreviations: ITT, Intent-to-Treat; NRS-A, Numeric Rating Scale of pain intensity score with activity; wWOCF, windowed worst observation carried forward.
Notes: p-values from Fisher's exact test. Exact 95% CI is based on Farrington-Manning score statistics.
Source: Table 14.2.14.

Based on NRS-A, fewer than half the subjects in the HTX-011 group (48.8%) experienced severe pain at any timepoint over 72 hours compared with 81.7% in the saline placebo group and 60.5% in the bupivacaine HCl group. These results are statistically significant.

Based on NRS-R, 36.0% of subjects in the HTX-011 group experienced severe pain at any time over 72 hours compared with 65.9% in the saline placebo group and 34.9% in the bupivacaine HCl group.

Overall, a large majority of subjects experienced moderate to severe (≥4) pain throughout 72 hours whatever the considered treatment group. This proportion was however lower in the HTX-011 group with statistical significance based on NRS-A and NRS-R.

Considering severe pain (≥7), the difference in proportion of subjects is statistically significant in favour of HTX-011 group based on NRS-A. However, there is no statistically significant difference between HTX-011 and bupivacaine group based on NRS-R and the proportion was slightly lower in the bupivacaine HCl group (36.0% versus 34.9 respectively).

Interestingly, it appears that, based on NRS-A and NRS-R, the proportion of subjects experiencing severe pain at any time over 72 hours did not or practically not progress after 24 hours even in the placebo group. This is in accordance with curves of mean NRS-A and NRS-R pain intensity scores over time (0-72 hours) showing higher pain intensity scores during the first hours post-surgery. At day 28, there was no significant difference in the proportion of subjects with NRS-A or NRS-R ≥7 but the proportion is lower in the bupivacaine group.

Applicant was requested to present proportions of patients with a NRS-A<4 at baseline, 12, 24 and 72 hours for studies 209 – cohort 2, 211, 301 and 302, and to consider these results in the discussion of the clinical relevance of treatment effects. Regarding study 302, treatment with HTX-011 results in a significant greater the proportion of patients with NRS-A score ≤ 4 at 12 and 24 hours. However, this was not the case at 72 hours. The justification of Applicant is that pain is expected to decrease for this surgery as it is seen in the placebo group with a proportion of about 60 % subjects with NRS-A score ≤ 4 at 72 hours. It could then be questioned the rational of using this surgery models to show significant efficacy for 72 hours even though it is expected that curve of pain scores over time have great probability to cross or to be very close at this time point as it is seen in this application for phase 3 studies (301 and 302). Overall, it seems that no firm conclusion can be drawn with these results at 72 hours (proportion of subjects with NRS-A score ≤ 4). The result at 12 and 24 hours are in line with previous results showing efficacy of Zynrelef the first day post-surgery.

Table 35: Incidence of Rescue Medication Use through 72 Hours (ITT Population)

	HTX-011 300 mg/9 mg (N=164)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=172)
Subjects who received rescue medication			
Any rescue medication	109 (66.5%)	74 (90.2%)	138 (80.2%)
Any opioid rescue medication	80 (48.8%)	64 (78.0%)	103 (59.9%)
Only non-opioid rescue medication	29 (17.7%)	10 (12.2%)	35 (20.3%)
Use of rescue medication by generic name			
Opioid rescue medications			
Oxycodone/oxycodone hydrochloride[a]	76 (46.3%)	62 (75.6%)	100 (58.1%)
Morphine/morphine sulfate[b]	38 (23.2%)	41 (50.0%)	42 (24.4%)
Fentanyl	2 (1.2%)	0	1 (0.6%)
Hydrocodone	1 (0.6%)	0	0
Non-opioid rescue medications			
Paracetamol	82 (50.0%)	50 (61.0%)	104 (60.5%)

Abbreviation: ITT, Intent-to-Treat.
Notes: Medications are coded to generic drug names using the World Health Organization Drug Dictionary Enhanced (WHODDE), Version 01 September 2016. At each level of summarization (any medication, generic drug name), subjects reporting use of more than one medication are counted only once.
[a] Subjects taking oxycodone and/or oxycodone hydrochloride were pooled.
[b] Subjects taking morphine and/or morphine sulfate were pooled.
Sources: Table 14.1.8.4, Table 14.1.8.2, Post Hoc Table 14.1.8.6

These results show a reduced proportion of subjects needing rescue medication in the HTX-011 group. There is a trend to higher use of paracetamol in the bupivacaine HCl group. Mean total and average use of paracetamol in HTX-011 and saline placebo groups seem quite similar.

The median time to the first use of opioid rescue medication during the 72-hour postoperative period was not evaluable (estimated beyond 72 hours for the HTX-011 group because over 50% of subjects did not require opioid rescue medication).

As requested, the applicant provided an analysis of time to first rescue medication (opioid and paracetamol). Overall, HTX-011 statistically significantly delayed the time to first use of opioid rescue medication compared to saline placebo and numerically delayed time to first use of rescue medication compared to bupivacaine HCl, which is satisfactory.

In addition, proportion of subjects who did not require any rescue medication through 72 hours was significantly increase with HTX-011 treatment compared to both control groups. However, large majority (> 65 %) of subjects required rescue medication which is an indicator that HTX-011 remains a treatment part of multimodal analgesia.

Table 36: Proportion of Subjects Who are Opioid-Free through Day 10 or Through Day 28 (ITT Population)

	HTX-011 300 mg/9 mg	Saline Placebo	Bupivacaine HCl 75 mg
All subjects	N=164	N=82	N=172
Opioid-free through Day 10	**80 (48.8%)**	**18 (22.0%)**	**67 (39.0%)**
Difference (95% CI) vs saline placebo	26.8% (12.6%, 38.1%)		
p-value vs saline placebo	<0.0001		
Difference (95% CI) vs bupivacaine HCl	9.8% (-0.9%, 20.5%)		
p-value vs bupivacaine HCl	0.0787		
Opioid-free through Day 28	**71 (43.3%)**	**17 (20.7%)**	**60 (34.9%)**
Difference (95% CI) vs saline placebo	22.6% (8.7%, 33.8%)		
p-value vs saline placebo	0.0007		
Difference (95% CI) vs bupivacaine HCl	8.4% (-2.3%, 18.8%)		
p-value vs bupivacaine HCl	0.1189		
Subjects who are opioid-free through 72 hours	n=84	n=18	n=69
Remained opioid-free through Day 10	80/84 (95.2%)	18/18 (100.0%)	67/69 (97.1%)
Remained opioid-free through Day 28	71/84 (84.5%)	17/18 (94.4%)	60/69 (87.0%)

Abbreviation: ITT, Intent-to-Treat.
Notes: Opioid-free through 72 hours is defined as having total morphine milligram equivalent (MME) opioid dose = 0 during the 72-hour on-site postoperative period, based on concomitant medication data. Opioid-free through Day 10 is defined as MME = 0 through 72 hours and answering "No" to the diary question "Did you take any opioid medication?" every day from 72 hours through Day 10. Opioid-free through Day 28 is defined similarly. Subjects who answered "Yes" or had a missing answer on any day during the period, or withdrew from the study during the period, were not considered opioid-free. 95% CIs are based on Farrington-Manning score statistics. P-values from Fisher's exact test.
Sources: Post Hoc Table 14.2.3.5, Post Hoc Table 14.2.3.6.

A large majority of opioid free subjects at 72 hours remained opioid free at day 10 and day 28. It would have been interesting to know if these subjects consumed others analgesic such as paracetamol or NSAID after discharge.

However, the number of patients who lost the analgesic effect during the period from 72 hours up to Day 10 and Day 28 was higher in HTX-011, what may indicate that HTX-011 is not superior to Bupivacaine HCl in maintenance of opioid-free status over the time. The applicant was requested to discuss this point. The applicant provided re-analysis on the opioid-free status of participants in Study 301 and Study 302, taking into account major findings during inspection, which revealed a systematic problem regarding errors in use of opioid diaries. There were numerous discrepancies between the post discharge opioid use data in patient diaries and data reported in the CSR. The results of re-analysis showed that proportion of subjects who were opioid-free and remained opioid-free through Day 10 was similar and through Day 28 was higher than in Bupivacaine HCl arm. Mean NRS-A Pain Scores at the Day 10 and Day 28 was lower in HTX-011 arm.

Phase 2b, Randomized, Double Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Infiltration for Postoperative Analgesia in Subjects Undergoing Total Knee Arthroplasty

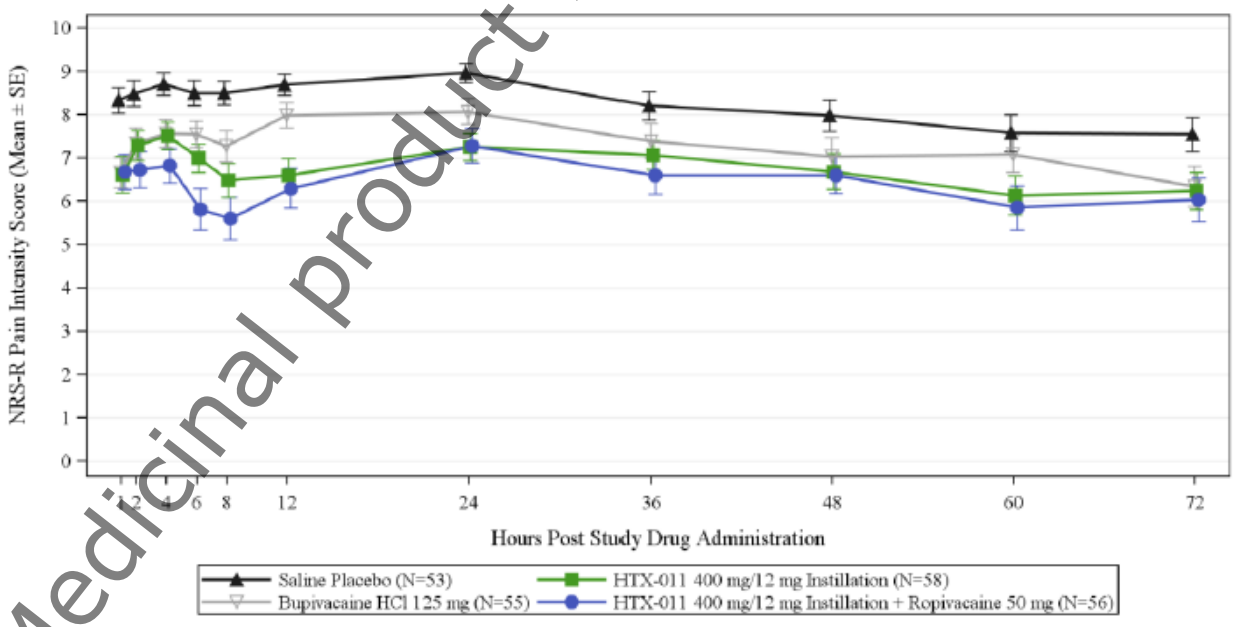
Methods

The study design was described in Section 2.5.1 of this report along with Cohort 1 results.

Cohort 2 results

The results for the primary and key secondary endpoints were statistically significant in favor of HTX-011 in Cohort 2. HTX-011 400 mg/12 mg administered with or without low-dose ropivacaine significantly reduced the mean AUC of NRS-R pain intensity scores over 48 hours (primary endpoint) and over 72 hours (key secondary endpoint) compared with saline placebo (primary comparison). Mean NRS-R pain scores were lower for the HTX-011 400 mg/12 mg group compared with saline placebo at all timepoints through 72 hours, with clear separation of the pain curves. Administration of low-dose ropivacaine into the posterior capsule provided a small additional benefit in postoperative analgesia during the first 8 hours. In addition, HTX-011 400 mg/12 mg with or without low-dose ropivacaine significantly reduced mean AUC of NRS-R pain scores over 24 hours compared with bupivacaine HCl. Mean AUC of NRS-R pain scores over 48 and 72 hours were also lower for both HTX-011 groups compared with bupivacaine HCl, and the differences were statistically significant for the HTX-011 400 mg/12 mg + low-dose ropivacaine group.

Figure 29: Mean NRS-R Pain Intensity Scores over time for HTX-011 vs Saline Placebo and Bupivacaine HCl in Cohort 2 (wWOCF, ITT Population)



Abbreviations: ITT, Intent-to-Treat; NRS-R, Numeric Rating Scale of pain intensity score at rest; wWOCF, windowed worst observation carried forward.
Source: Figure 14.2.3.2.

Table 37: Mean AUC0-48 and AUC0-72 of NRS-R Pain Intensity Scores for HTX-011 compared with saline placebo in cohort 2 (wWOCF, ITT Population)

Treatment Group	N	Mean (SD)	p-value vs Saline Placebo
AUC_{0-48} of NRS-R (primary endpoint)			
HTX-011 400 mg/12 mg + low-dose ropivacaine	56	307.25 (127.674)	<0.0001
HTX-011 400 mg/12 mg	58	322.08 (99.669)	0.0002
Saline placebo	53	396.36 (77.468)	
AUC_{0-72} of NRS-R (key secondary endpoint)			
HTX-011 400 mg/12 mg + low-dose ropivacaine	56	452.54 (194.095)	<0.0001
HTX-011 400 mg/12 mg	58	471.19 (149.443)	0.0004
Saline placebo	53	577.93 (125.102)	

Abbreviations: AUC, area under the curve; ITT, Intent-to Treat; NRS-R, Numeric Rating Scale of pain intensity score at rest; wWOCF, windowed worst observation carried forward.
Notes: p-values reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect.
Sources: Table 14.2.1.1.2, Table 14.2.1.5.2.

Table 38: Mean AUC0-48 and AUC0-72 of NRS-R Pain Intensity Scores for HTX-011 compared with bupivacaine HCl in Cohort 2 (wWOCF, ITT Population)

Treatment Group	N	Mean (SD)	p-value vs Bupivacaine HCl
AUC_{0-48} of NRS-R			
HTX-011 400 mg/12 mg + low-dose ropivacaine	56	307.25 (127.674)	0.0212
HTX-011 400 mg/12 mg	58	322.08 (99.669)	0.1160
Bupivacaine HCl 125 mg	55	352.74 (100.887)	
AUC_{0-72} of NRS-R			
HTX-011 400 mg/12 mg + low-dose ropivacaine	56	452.54 (194.095)	0.0325
HTX-011 400 mg/12 mg	58	471.19 (149.443)	0.1246
Bupivacaine HCl 125 mg	55	516.93 (152.512)	

Abbreviations: AUC, area under the curve; ITT, Intent-to Treat; NRS-R, Numeric Rating Scale of pain intensity score at rest; wWOCF, windowed worst observation carried forward.
Notes: p-values reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect.
Sources: Table 14.2.1.1.2, Table 14.2.1.5.2.

This study in cohort 2 shows positive results on the primary endpoint (mean AUC0-48 of NRS-R Pain Intensity Scores) and on the key secondary endpoint (mean AUC0-72 of NRS-R Pain Intensity Scores) for HTX-011 compared with saline placebo. In terms of pain scores over time, the difference seems close to 2 on 10-point scale. It should be noted that NRS-R was not the criteria selected for the phase 3 studies where NRS-A was utilized.

However, to show significant results on mean AUC0-48 and mean AUC0-72 of NRS-R Pain Intensity Scores for HTX-011 compared to bupivacaine HCl, it was necessary to add 50 mg of ropivacaine. In fact, graphically, the higher difference in pain scores between HTX-011 and saline placebo occurred in the first 8 hours in the HTX-011 + ropivacaine group, when the ropivacaine is active.

Pain intensity was also assessed with activity and the results were consistent with the NRS-R results.

HTX-011 significantly reduced mean AUC of NRS-A pain intensity scores on every time intervals compared to saline placebo (AUC0-24, AUC0-48 and AUC0-72).

HTX-011 significantly reduced mean AUC of NRS-A pain intensity scores over 24 and 48 hours compared to bupivacaine HCl (AUC0-24, AUC0-48).

The difference on mean NRS-A Pain Intensity Scores over time seems close to 1 on 10-point scale. The reduction of pain scores after 24 hours post-dose in HTX-011 group compared to saline placebo seems limited. Overall, pain remains severe (≥7/10) in all treatment groups.

According to the selected criteria (AUC0-48 and AUC0-72 of NRS-R pain intensity scores), over a 72 hours period, HTX-011 does not seem to provide a significant better analgesia than bupivacaine HCl.

The applicant was requested to justify the effect of Zynrelef on pain to achieve clinically significant pain reduction for 72 hours. It should be noted that the results provided in the HTX-011 + ropivacaine group were not taken into consideration because ropivacaine has an additional analgesic effect that prevents assessment of HTX-011 analgesic effect considering ropivacaine was not added in the two other groups. The applicant justified that the study was not intended, nor powered, to demonstrate superiority to bupivacaine HCl. However, CHMP disagreed with the applicant's assumption that it is not necessary to formally demonstrate non-inferiority to the active comparator in this particular case.

Indeed, in TKA study, the primary and key secondary endpoint only considered a comparison against placebo. This is not considered sufficient as the criteria of AUC of pain intensity scores has no direct clinical translation and the minimum difference that would be considered as clinically significant when comparing AUC has not been justified.

All subjects except 2 (1 in the HTX-011 400 mg/12 mg + low-dose ropivacaine group and 1 in the bupivacaine HCl group) were administered rescue medication during the 72-hour postoperative period.

Table 39: Total Postoperative Opioid Consumption (MME) From 0 through 24, 48, and 72 Hours in Cohort 2 (ITT Population)

	Saline Placebo (N=53)	Bupivacaine HCl 125 mg (N=55)	HTX-011 400 mg/12 mg (N=58)	HTX-011 400 mg/12 mg + low-dose ropivacaine (N=56)
Opioid consumption through 24 hours				
Mean (SD)	39.09 (19.215)	32.62 (15.232)	28.79 (14.031)	26.43 (14.191)
Median (min, max)	38.00 (5.0, 82.0)	30.00 (0.0, 71.0)	27.75 (2.5, 74.0)	26.00 (0.0, 66.0)
p-value vs saline placebo			0.0032	0.0003
p-value vs bupivacaine HCl			0.1584	0.0461
Opioid consumption through 48 hours				
Mean (SD)	58.45 (27.928)	52.56 (22.646)	48.75 (21.859)	45.41 (25.508)
Median (min, max)	56.00 (5.0, 114.0)	50.00 (0.0, 108.0)	48.50 (2.5, 105.0)	43.00 (0.0, 133.5)
p-value vs saline placebo			0.0532	0.0091
p-value vs bupivacaine HCl			0.4431	0.0611
Opioid consumption through 72 hours				
Mean (SD)	73.55 (34.448)	68.35 (29.169)	64.39 (27.889)	60.32 (34.949)
Median (min, max)	73.00 (10.0, 158.0)	70.00 (0.0, 147.5)	63.25 (2.5, 123.0)	60.25 (0.0, 188.5)
p-value vs saline placebo			0.1617	0.0253
p-value vs bupivacaine HCl			0.5560	0.1371

Abbreviations: ITT, Intent-to Treat; MME, morphine milligram equivalent.
Notes: Opioid rescue medications include hydrocodone, morphine, oxycodone, and pethidine. P-values were obtained using the Wilcoxon rank sum test.
Sources: Table 14.2.2.1.2, Table 14.2.2.2.2.

Overall, opioid sparing effect in this surgical model seems limited. HTX-011 without ropivacaine only reduced significantly median opioid consumption over the first 24 hours compared to placebo. Numerically, HTX-011 shows an opioid sparing effect of approximately 10 mg/72 hours compared to placebo (reduction of about 12.5 % on mean total opioid consumption through 72 hours). As a comparison, it has been reported that analgesic techniques, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase 2 (COX-2) inhibitors, acetaminophen, ketamine, gabapentin and pregabalin, and regional anesthetic techniques provide 20–50% opioid sparing in the postoperative setting. In addition, no significant sparing effect of HTX-011 compared to bupivacaine HCl can be highlighted (opioid consumption over 24, 48 and 72 hours). There was also no significant difference in proportion of subjects having used opioids according to the applicant.

The applicant was requested to justify clinical significance of the opioid sparing effect and a small opioid sparing effect with a 13.4% greater reduction in opioid use through 72 hours post-dose in HTX-011 compared with saline placebo, and a 9.6% greater reduction compared with bupivacaine HCl. This effect was not associated with a decrease in prespecified ORAEs and is not considered as clinically significant.

The objective to provide a better pain relief (with a longer-lasting postoperative bupivacain and as a consequence to reduce the need for opioids after surgery) compared to the defined standard of care bupivacaine HCl is not fully achieved.

A confirmatory phase 3 study in this surgery, using at least a comparison to bupivacaine at a decreased dose (compared to Zynrelef) as a primary or a key secondary endpoint (as what was done in the two phase 3 studies) is regarded as minimally requested.

Finally, this study in another surgical model leads to not consider surgical models as one entity. Therefore, pain management should be adapted to the type of surgical model, even if the multimodal approach will be the corner stone. Specificities linked to the type of surgical models have to be considered before to claim a broad indication in "post-operative pain management".

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 40: Summary of efficacy for Study 301 in bunionectomy

Title: A Phase 3, Randomized, Double-Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Local Administration for Postoperative Analgesia and Decreased Opioid Use Following Unilateral Simple Bunionectomy		
Study identifier	HTX-011-301	
Design	Multicenter (USA), Parallel, Single-dose, Randomized, Double-Blind, Saline Placebo- and Active-Controlled	
	Duration of surgery phase:	On Day 1, subjects underwent a bunionectomy. The start of study drug administration (intraoperatively) was considered Time 0 (Day 1).
	Duration of postanesthesia phase:	72 hours. Postoperative assessments following surgery and immediate postoperative recovery
	Duration of ambulatory phase:	38 days After the 72-hour assessments were completed, subjects could be discharged. From discharge through Day 28 : opioid medication recording on daily diary Day 10 and Day 28 : follow-up assessments on study site Day 42 : safety follow-up (X-Ray) on study site
Hypothesis	Superiority	
Treatments groups	HTX-011 via instillation into the surgical site (2.1 mL) Bupivacaine 60 mg / Meloxicam 1.8 mg	Single dose, Day 1 164 subjects randomized
	Saline Placebo via instillation into the surgical site (2.1 mL)	Single dose, Day 1 109 subjects randomized
	Bupivacaine HCl 0.5% via injection into the surgical site (50 mg, 10 mL)	Single dose, Day 1 165 subjects randomized

Endpoints and definitions	Primary endpoint	AUC_{0-72} of the NRS-A Pain Intensity Scores	Mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) through 72 hours (AUC_{0-72}) for HTX-011 compared with saline placebo
	1st Key Secondary endpoint	AUC_{0-72} of the NRS-A Pain Intensity Scores	Mean AUC_{0-72} of the NRS-A pain intensity scores for HTX-011 compared with bupivacaine HCl
	2nd Key Secondary endpoint	Opioid consumption through 72 hours (MME)	Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with saline placebo
	3nd Key Secondary endpoint	Opioid-free through 72 hours	Proportion of subjects who are opioid-free through 72 hours for HTX-011 compared with bupivacaine HCl
	4th Key Secondary endpoint	Opioid consumption through 72 hours (MME)	Mean total postoperative opioid consumption (in morphine milligram equivalents) through 72 hours for HTX-011 compared with bupivacaine HCl
Database lock			

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat population: All subjects who were randomized and received study drug (N=412). This population was used as the primary analysis population for all efficacy endpoints. The randomized treatment assignment was used for analysis in this population.			
Descriptive statistics and estimate variability	Treatment group	HTX-011	Placebo	Bupivacaine HCl
	Number of subject	157	100	155
	AUC_{0-72} of the NRS-A Pain Intensity Scores			
	Mean (SD)	323.29 (182.641)	445.34 (155.792)	393.5 (153.756)
	Opioid consumption through 72 hours (MME)			
	Mean (SD) Median (Min, Max)	18.80 (19.801) 12.50 (0.0, 83.0)	30.06 (21.016) 25.00 (0.0, 80.0)	25.09 (21.553) 17.50 (0.0, 92.5)
	Opioid-free through 72 hours			
	N (%)	45 (28.7)	2 (2.0)	17 (11.0)

Effect estimate per comparison	AUC_{0-72} of the NRS-A Pain Intensity Scores	Comparison groups	HTX-011 vs Placebo	HTX-011 vs Bupivacaine HCl
		LSMD (SE)	-122.05 (21.217)	-70.16 (18.777)
		[95% CI]	[-163.76, -80.34]	[-107.07, -33.25]
		P-value (ANOVA)	<0.0001	0.0002
	Opioid consumption through 72 hours (MME)	Comparison groups	HTX-011 vs Placebo	HTX-011 vs Bupivacaine HCl
		P-value (Wilcoxon rank sum test)	<0.0001	0.0022
	Opioid-free through 72 hours	Comparison groups	HTX-011 vs Placebo	HTX-011 vs Bupivacaine HCl
		Difference (%)	26.7 %	17.7 %
		[95% CI]	[18.6%, 34.7%]	[8.5%, 26.5%]
		P-value (Fisher's exact test)	<0.0001	0.0001
Notes				

Table 41: Summary of efficacy for Study 302 in herniorrhaphy

Title: A Phase 3, Randomized, Double-Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Local Administration for Postoperative Analgesia and Decreased Opioid Use Following Unilateral Open Inguinal Herniorrhaphy		
Study identifier	HTX-011-302	
Design	Multicenter (USA + Belgium), Parallel, Single-dose, Randomized, Double-Blind, Saline Placebo- and Active-Controlled	
	Duration of surgery phase:	On Day 1, subjects underwent a herniorrhaphy. The start of study drug administration (intraoperatively) was considered Time 0 (Day 1).
	Duration of postanesthesia phase:	72 hours. Postoperative assessments following surgery and immediate postoperative recovery

	Duration of ambulatory phase:		24 days After the 72-hour assessments were completed, subjects could be discharged. From discharge through Day 28 : opioid medication recording on daily diary Day 10 and Day 28 : follow-up assessments on study site
Hypothesis	Superiority		
Treatments groups	HTX-011 via instillation into the surgical site (10.3 mL) Bupivacaine 300 mg / Meloxicam 9 mg		Single dose, Day 1 178 subjects randomized
	Saline Placebo via instillation into the surgical site (10.3 mL)		Single dose, Day 1 89 subjects randomized
	Bupivacaine HCl 0.25% via injection into the surgical site (75 mg, 30 mL)		Single dose, Day 1 179 subjects randomized
Endpoints and definitions	Primary endpoint	AUC_{0-72} of the NRS-A Pain Intensity Scores	Mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) through 72 hours (AUC_{0-72}) for HTX-011 compared with saline placebo
	1st Key Secondary endpoint	AUC_{0-72} of the NRS-A Pain Intensity Scores	Mean AUC_{0-72} of the NRS-A pain intensity scores for HTX-011 compared with bupivacaine HCl
	2nd Key Secondary endpoint	Opioid consumption through 72 hours (MME)	Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with saline placebo
	3nd Key Secondary endpoint	Opioid-free through 72 hours	Proportion of subjects who are opioid-free through 72 hours for HTX-011 compared with bupivacaine HCl
	4th Key Secondary endpoint	Opioid consumption through 72 hours (MME)	Mean total postoperative opioid consumption (in morphine milligram equivalents) through 72 hours for HTX-011 compared with bupivacaine HCl
Database lock			

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat population: All subjects who were randomized and received study drug (N=418). This population was used as the primary analysis population for all efficacy endpoints. The randomized treatment assignment was used for analysis in this population.			
Descriptive statistics and estimate variability	Treatment group	HTX-011	Placebo	Bupivacaine HCl

	Number of subject	164	82	172
	AUC_{0-72} of the NRS-A Pain Intensity Scores			
	Mean (SD)	269.39 (173.719)	350.82 (171.224)	341.88 (158.303)
	Opioid consumption through 72 hours (morphine milligram equivalent)			
	Mean (SD) Median (Min, Max)	10.85 (17.062) 0.00 (0.0, 103.0)	17.53 (18.908) 11.25 (0.0, 73.5)	14.51 (18.185) 7.25 (0.0, 87.5)
	Opioid-free through 72 hours			
	N (%)	84 (51.2)	18 (22.0)	69 (40.1)

Effect estimate per comparison	AUC_{0-72} of the NRS-A Pain Intensity Scores	Comparison groups	HTX-011 vs Placebo	HTX-011 vs Bupivacaine HCl
		LSMD (SE)	-81.43 (22.592)	-72.49 (18.230)
		[95% CI]	[-125.83, -37.02]	[-108.32, -36.65]
		P-value (ANOVA)	0.0004	<0.0001
	Opioid consumption through 72 hours (morphine milligram equivalent)	Comparison groups	HTX-011 vs Placebo	HTX-011 vs Bupivacaine HCl
		P-value (Wilcoxon rank sum test)	0.0001	0.0240
	Opioid-free through 72 hours	Comparison groups	HTX-011 vs Placebo	HTX-011 vs Bupivacaine HCl
		Difference (%)	29.3 %	11.1 %
		[95% CI]	[15.6%, 40.5%]	[0.3%, 21.8%]
		P-value (Fisher's exact test)	<0.0001	0.0486
Notes				

Analysis performed across trials (pooled analyses and meta-analysis)

No pooled analysis and meta-analysis were performed.

Clinical studies in special populations

No clinical studies were performed in special population.

Supportive study

Mammoplasty: study 211

"Phase 2b, Randomized, Controlled Study of HTX-011 Administered Via Pectoral Nerve Block in Subjects Undergoing Upper Extremity Surgery for Augmentation Mammoplasty"

This study was designed to evaluate the analgesic efficacy, safety, and pharmacokinetics (PK) of HTX-011 of HTX-011 administered as a single dose via nerve block (NB) or via instillation in subjects undergoing augmentation mammoplasty.

The study included 4 cohorts. HTX-011 was administered via bilateral ultrasound guided lateral and medial pectoral nerve block (NB) before surgery in Cohorts 1 through 4 and also via instillation into the surgical site prior to the end of surgery in Cohort 4. Increasing doses of HTX-011 were used in each cohort, after review of planned interim analyses of data from the previous cohort.

Saline placebo and bupivacaine HCl 0.25% (50 mg) administered via NB were used as control.

Study assessments

Efficacy was assessed based on pain intensity (NRS-R and NRS-A), use of opioid rescue medication, Patient Global Assessment (PGA) of pain control, discharge readiness per the Modified Postanaesthetic Discharge Scoring System (MPADSS), the subject's satisfaction with pain control, and an overall benefit of analgesia score (OBAS).

Safety was assessed based on AEs, clinical laboratory tests, physical examinations, wound healing, vital sign measurements, continuous Holter monitoring, motor function, and sensory function.

Serial blood samples were collected for bupivacaine and meloxicam PK analysis.

Main inclusion criteria

Subjects were adult female with scheduled primary bilateral submuscular augmentation mammoplasty with saline or silicone smooth implants with a volume of 300 to 500 cc, inclusive.

Main exclusion criteria

Subjects had another planned concurrent surgical procedure (eg, mastopexy) or a planned reconstructive procedure status post breast cancer therapy, a medical condition expected to require analgesic treatment in the postoperative period or that would confound postoperative pain assessments, use of NSAIDS within 10 days of surgery or had taken long acting opioids within 3 days of surgery, or had taken any opioids within 24 hours of scheduled surgery for this study.

Treatments

Cohort 1: approximately 24 subjects were to be randomized to 1 of the following 3 treatment groups in a 2:1:1 ratio:

- HTX-011 60 mg/1.8 mg (2.1 mL volume administered) via NB.

- Bupivacaine HCl without epinephrine 0.25% (50 mg, 20 mL) via NB.
- Saline placebo (2.1 mL) via NB.

Cohort 2: approximately 48 subjects were to be randomized to 1 of the following 3 treatment groups in a 2:1:1 ratio:

- HTX-011 (a single dose recommended by the IRC of 120 mg/3.6 mg, 4.1 mL) via NB.
- Bupivacaine HCl without epinephrine 0.25% (50 mg, 20 mL) via NB.
- Saline placebo (4.1 mL) via NB.

Ropivacaine HCl 0.5% 5 mL was administered in each of the surgical incision lines at closure in all treatment groups.

Cohort 3: approximately 48 subjects were to be randomized to 1 of the following 3 treatment groups in a 2:1:1 ratio:

- HTX-011 (a single dose recommended by the IRC of 240 mg/7.2 mg, 8.2 mL) via NB.
- Bupivacaine HCl without epinephrine 0.25% (50 mg, 20 mL) via NB.
- Saline placebo (8.2 mL) via NB.

Ropivacaine HCl 0.5% 5 mL was administered in each of the surgical incision lines at closure in all treatment groups.

Cohort 4: approximately 120 subjects were to be randomized to 1 of the following 4 treatment groups in a 4:4:1:1 ratio:

- HTX-011 (a single dose recommended by the IRC of 400 mg/12 mg, 13.7 mL) via NB.
- HTX-011 (a single dose recommended by the IRC of 400 mg/12 mg, 13.7 mL) via instillation into the intended space for the implant, with 200 mg/6 mg (6.8 mL) per side; saline placebo (13.7 mL) via NB for masking.
- Bupivacaine HCl without epinephrine 0.25% (50 mg, 20 mL) via NB.
- Saline placebo (13.7 mL) via NB.

Ropivacaine HCl 0.5% 5 mL was administered in each of the surgical incision lines at closure in all treatment groups.

The surgical procedure was conducted under general anesthesia.

Subjects in Cohorts 2 and 4, and optionally in Cohort 3, received fentanyl 50 µg intravenously (IV) just prior to the end of the surgery in order to decrease the inherent variability of intraoperative pain control on immediate postoperative pain. In Cohorts 2, 3, and 4, subjects were administered 5 mL of 0.5% ropivacaine HCl in each of the surgical incision lines at closure.

Rescue medication during 72 hours after study drug administration was allowed to subjects with inadequately controlled pain symptoms. The rescue medications were the following:

- oral (PO) immediate-release oxycodone (≤10 mg within a 4-hour period as needed)

- IV morphine (≤10 mg within a 4-hour [Cohort 1] or 2-hour [Cohorts 2, 3, and 4] period)

After 72 hours, the analgesic regimen could be adjusted for each subject individually as deemed appropriate by the physician responsible for the postoperative care.

Main study objectives

Primary: to compare the efficacy and duration of analgesia following bilateral ultrasound-guided lateral and medial pectoral nerve block with HTX-011 to bupivacaine HCl without epinephrine and saline placebo in subjects undergoing upper extremity surgery.

Main secondary objectives:

- To evaluate the efficacy and duration of analgesia for HTX-011 administered using different techniques in this study population.
- To evaluate additional efficacy parameters in this study population.
- To characterize the bupivacaine and meloxicam PK profiles of HTX-011 in this study population.
- To determine the optimal administration technique of HTX-011 in this surgical model.
- To further assess the safety and tolerability of HTX-011 in this study population.

Main efficacy endpoints

The primary endpoint was the mean area under the curve (AUC) of the NRS-A pain-intensity scores through 24 hours (AUC0-24).

Main secondary endpoints included mean total postoperative opioid consumption (in morphine equivalents) through 24, 48, and 72 hours, median time in hours to first opioid rescue administration through 72 hours, mean AUC of the NRS-A and NRS-R pain-intensity scores at different intervals (0-6, 0-12, 12-24, 24-48, 0-48, 48-72, and 0-72 hours) and mean NRS-A and NRS-R pain-intensity scores at each assessed timepoint.

Study subjects

A total of 251 subjects were randomized and 243 received study drug. The majority of the randomized subjects (88.8%) were recruited at one of the three study sites. The demographics and baseline characteristics were generally well balanced across treatment groups. The mean (SD) age was 31.2 (8.01). Mean (SD) across treatment groups was 23.66 (3.418). All 243 subjects completed the 72-hour postoperative observation period and 93.8% completed the study.

Main results in cohort 1, 2, 3

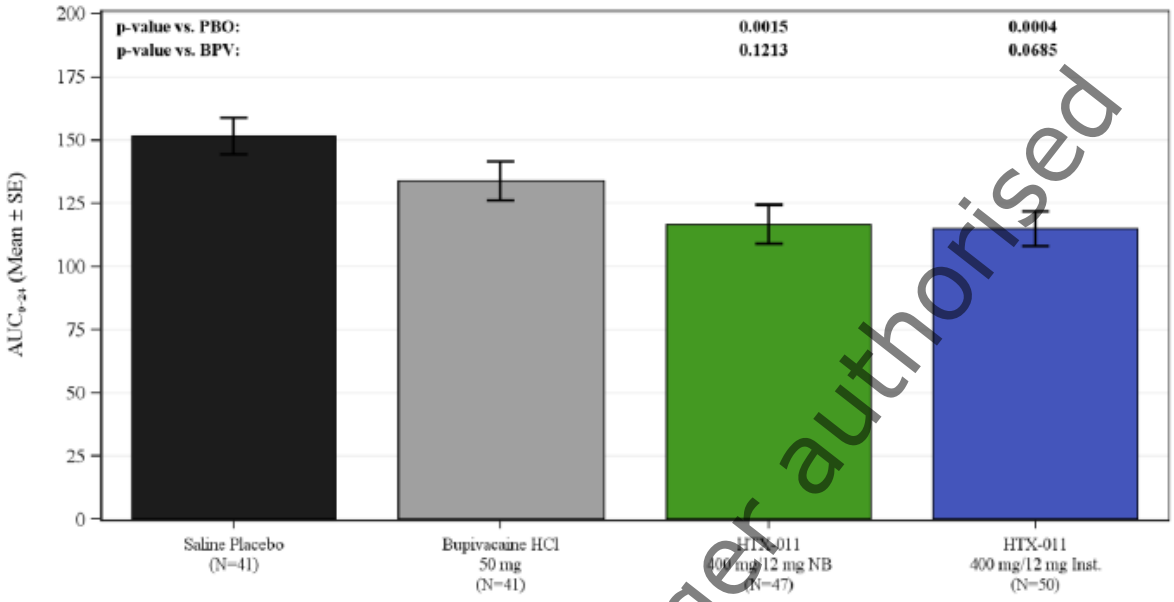
According to the applicant, the lower HTX-011 doses (60 mg/1.8 mg to 240 mg/7.2 mg) via NB did not significantly reduce postoperative pain compared with either control group. As a consequence, provided results are focused on the cohort 4.

Main results in cohort 4

The primary comparison on the primary endpoint for each HTX-011 group was against the pooled saline placebo group. Comparisons of HTX-011 against the pooled bupivacaine HCl were considered secondary comparisons.

Both HTX-011 400 mg/12 mg groups, NB and instillation, had significantly lower mean AUC0-24 of the NRS-A pain-intensity scores compared with saline placebo via NB (primary endpoint, wWOCF). Compared with bupivacaine HCl via NB, both HTX-011 400 mg/12 mg treatment groups had lower mean AUC0-24 of the NRS-A pain-intensity scores but these differences were not statistically significant.

Figure 30: Mean (SE) AUC0-24 of the NRS-A Pain-Intensity Scores using wWOCF (mITT Population)

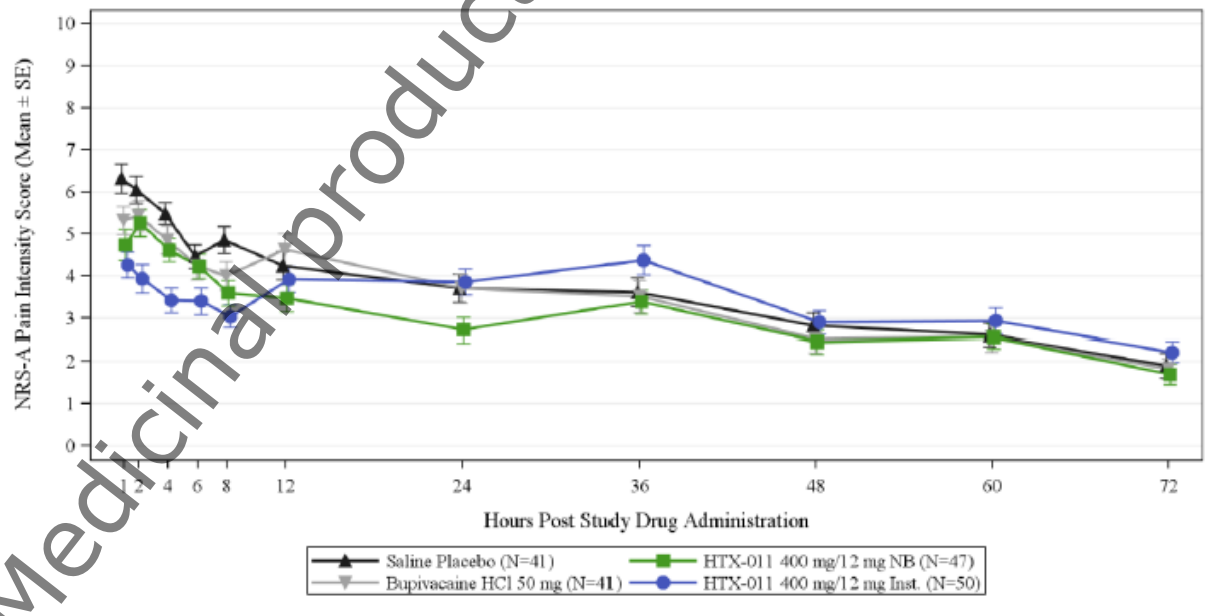


Abbreviations: ANOVA, analysis of variance; AUC, area under the curve; BPV, bupivacaine HCl; Inst., Instillation; mITT, modified Intent-to-Treat; NB, bilateral ultrasound guided lateral and medial pectoral nerve block; NRS-A, Numeric Rating Scale of pain-intensity score with activity; PBO, saline placebo; wWOCF, windowed worst observation carried forward.

Note: p-values reflect results of an ANOVA with randomized treatment as the main effect

Source: Table 14.2.1.1.

Figure 31: Mean NRS-A of Pain-Intensity Scores at Each Assessed Timepoint through 72 Hours Using LOCF (mITT Population)



Abbreviations: Inst., instillation; mITT, modified Intent-to-Treat; NB bilateral ultrasound guided lateral and medial pectoral nerve block; NRS-A, Numeric Rating Scale of pain-intensity score with activity; LOCF, last observation carried forward.

Source: Table 14.2.5.4.

Table 42: Mean AUC of NRS-A Pain-Intensity Scores at Each Interval (wWOCF, mITT Population)

HTX-011 Dose Group	N	Mean (SD)	Control	N	Mean (SD)	P-value[a]
AUC_{0-6}						
400 mg/12 mg NB	47	27.46 (10.082)	Saline placebo	41	33.79 (9.688)	0.0036
			Bupivacaine HCl 50 mg	41	30.81 (11.143)	0.1430
400 mg/12 mg Instillation	50	22.87 (11.985)	Saline placebo	41	33.79 (9.688)	<0.0001
			Bupivacaine HCl 50 mg	41	30.81 (11.143)	0.0017
AUC_{0-12}						
400 mg/12 mg NB	47	59.38 (22.767)	Saline placebo	41	74.52 (21.249)	0.0019
			Bupivacaine HCl 50 mg	41	64.68 (22.626)	0.2776
400 mg/12 mg Instillation	50	51.34 (23.388)	Saline placebo	41	74.52 (21.249)	<0.0001
			Bupivacaine HCl 50 mg	41	64.68 (22.626)	0.0073
AUC_{12-24}						
400 mg/12 mg NB	47	57.33 (31.824)	Saline placebo	41	77.00 (27.213)	0.0027
			Bupivacaine HCl 50 mg	41	69.15 (28.598)	0.0721
400 mg/12 mg Instillation	50	63.53 (28.295)	Saline placebo	41	77.00 (27.213)	0.0239
			Bupivacaine HCl 50 mg	41	69.15 (28.598)	0.3505
AUC_{0-48}						
400 mg/12 mg NB	47	227.29 (107.465)	Saline placebo	41	290.16 (95.572)	0.0050
			Bupivacaine HCl 50 mg	41	262.34 (107.910)	0.1314
400 mg/12 mg Instillation	50	245.82 (92.918)	Saline placebo	41	290.16 (95.572)	0.0278
			Bupivacaine HCl 50 mg	41	262.34 (107.910)	0.4349
AUC_{0-72}						
400 mg/12 mg NB	47	324.10 (171.125)	Saline placebo	41	392.02 (153.871)	0.0549
			Bupivacaine HCl 50 mg	41	362.17 (168.845)	0.2979
400 mg/12 mg Instillation	50	362.48 (145.685)	Saline placebo	41	392.02 (153.871)	0.3507
			Bupivacaine HCl 50 mg	41	362.17 (168.845)	0.9924

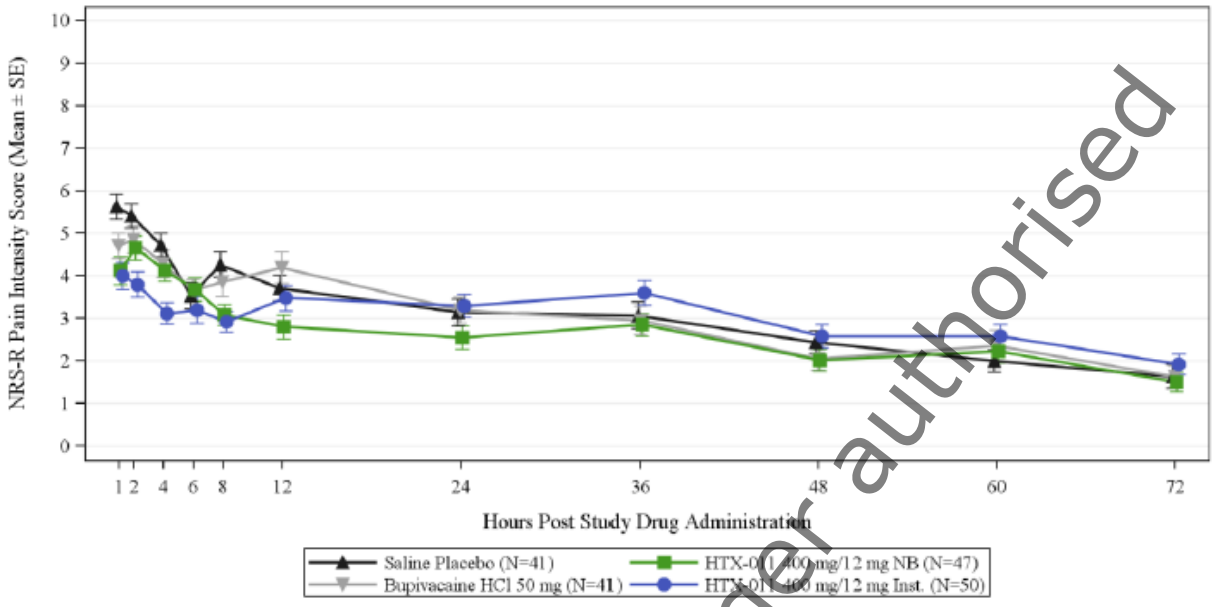
Abbreviations: ANOVA, analysis of variance; AUC, area under the curve; LSMD, least squares mean difference; mITT, modified Intent-to-Treat; NB bilateral ultrasound guided lateral and medial pectoral nerve block; NRS-A, Numeric Rating Scale of pain-intensity score with activity; PI, pain intensity; wWOCF, windowed worst observation carried forward.

Note: PI collections occur at 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours post-surgery.

[a] Statistics reflect results of an ANOVA.

Source: Table 14.2.3.1.

Figure 32: Mean (SE) NRS-R of Pain-Intensity Scores at each assessed timepoint through 72 hours using LOCF (mITT Population)



Abbreviations: Inst., instillation; mITT, modified Intent-to-Treat; NB, bilateral ultrasound guided lateral and medial pectoral nerve block; NRS-R, Numeric Rating Scale of pain-intensity score at rest; wWOCF, windowed worst observation carried forward.

Source: Table 14.2.6.3

Table 43: Mean AUC of NRS-R Pain-Intensity Scores at Each Interval (wWOCF, mITT Population)

HTX-011 Dose Group	N	Mean (SD)	Control	N	Mean (SD)	P-value
AUC_{0-6}						
400 mg/12 mg NB	47	25.17 (9.644)	Saline placebo	41	30.89 (9.526)	0.0065
			Bupivacaine HCl 50 mg	41	27.87 (10.330)	0.2097
400 mg/12 mg Instillation	50	20.73 (10.666)	Saline placebo	41	30.89 (9.526)	<0.0001
			Bupivacaine HCl 50 mg	41	27.87 (10.330)	0.0018
AUC_{0-12}						
400 mg/12 mg NB	47	53.42 (22.107)	Saline placebo	41	67.23 (20.951)	0.0036
			Bupivacaine HCl 50 mg	41	59.73 (19.898)	0.165
400 mg/12 mg Instillation	50	47.69 (21.593)	Saline placebo	41	67.23 (20.951)	<0.0001
			Bupivacaine HCl 50 mg	41	59.73 (19.898)	0.0074
AUC_{12-24}						
400 mg/12 mg NB	47	51.48 (28.822)	Saline placebo	41	66.65 (26.991)	0.0130
			Bupivacaine HCl 50 mg	41	63.99 (25.872)	0.0360
400 mg/12 mg Instillation	50	56.78 (25.831)	Saline placebo	41	66.65 (26.991)	0.0792
			Bupivacaine HCl 50 mg	41	63.99 (25.872)	0.1893
AUC_{0-48}						
400 mg/12 mg NB	47	201.75 (97.586)	Saline placebo	41	254.47 (91.177)	0.0108
			Bupivacaine HCl 50 mg	41	242.11 (96.071)	0.0545
400 mg/12 mg Instillation	50	220.71 (86.133)	Saline placebo	41	254.47 (91.177)	0.0733
			Bupivacaine HCl 50 mg	41	242.11 (96.071)	0.2660
AUC_{0-72}						
400 mg/12 mg NB	47	286.73 (158.195)	Saline placebo	41	341.44 (145.152)	0.0963
			Bupivacaine HCl 50 mg	41	332.27 (150.952)	0.1724
400 mg/12 mg Instillation	50	326.84 (136.384)	Saline placebo	41	341.44 (145.152)	0.6226
			Bupivacaine HCl 50 mg	41	332.27 (150.952)	0.8575

Abbreviations:; mITT, modified Intent-to-Treat; NB bilateral ultrasound guided lateral and medial pectoral nerve block; NRS-R, Numeric Rating Scale of pain-intensity score at rest; wWOCF, windowed worst observation carried forward.

Source: Table 14.2.4.1.

Table 44: Total Postoperative Opioid Consumption in Morphine Equivalents through 24, 48, and 72 Hours (mITT Population)

	Saline Placebo via NB (N=41)	Bupivacaine HCl 50 mg via NB (N=41)	400 mg/12 mg via NB (N=47)	HTX-011 400 mg/ 12 mg via Instillation (N=50)
0-24 hours				
Mean (SD)	19.00 (11.288)	17.07 (9.681)	14.04 (9.823)	12.79 (7.898)
Median (Min, Max)	17.50 (2.0, 40.5)	15.00 (0.0, 36.0)	11.00 (0.0, 40.0)	10.00 (2.0, 33.5)
p-value[a] vs saline placebo			0.0435	0.0093
p-value[a] vs bupivacaine HCl			0.1762	0.0455
0-48 hours				
Mean (SD)	29.44 (17.874)	26.62 (16.696)	22.13 (16.272)	26.43 (14.341)
Median (Min, Max)	27.50 (2.0, 75.5)	22.00 (0.0, 65.0)	17.50 (0.0, 58.0)	25.00 (2.0, 69.0)
p-value[a] vs saline placebo			0.0575	0.5363
p-value[a] vs bupivacaine HCl			0.2480	0.9269
0-72 hours				
Mean (SD)	36.38 (23.275)	32.57 (23.088)	28.84 (22.603)	37.46 (21.452)
Median (Min, Max)	32.50 (2.0, 93.0)	27.00 (0.0, 97.0)	23.00 (0.0, 89.0)	35.00 (2.0, 91.5)
p-value[a] vs saline placebo			0.1073	0.7406
p-value[a] vs bupivacaine HCl			0.3338	0.3167

Abbreviations: mITT, modified Intent-to-Treat; NB, bilateral ultrasound guided lateral and medial pectoral nerve block.
Note: Opioid rescue medication includes morphine and oxycodone.
[a] p-value is from the Wilcoxon Rank-Sum test.
Source: Table 14.2.2.1 and Table 14.2.2.2.

This study in cohort 4 shows positive results for HTX-011 400 mg/12 mg, administered as a single dose via nerve block (NB) or via instillation, on the primary endpoint (mean AUC0-24 of the NRS-A pain-intensity scores) compared with saline placebo. Compared with bupivacaine HCl via NB, both HTX-011 400 mg/12 mg treatment groups had lower mean AUC0-24 of the NRS-A pain-intensity scores but these differences were not statistically significant.

After 24 hours post-dose, there is no clinically meaningful difference in pain scores between HTX-011 400 mg/12 mg and both control groups.

Mean and median total opioid consumption in MME over 72 hours were numerically higher in HTX-011 400 mg/12 mg administered via instillation compared to both control groups.

These results seem not sufficient to support an indication to reduce postoperative pain for 72 hours in augmentation mammoplasty.

The applicant justified that the study was only exploratory and not designed for comparative assessment of HTX-011 administered via instillation as the comparators (saline placebo and bupivacaine HCl) were administered via nerve block but supports the activity of HTX-011 in an additional soft tissue model as reduction in mean AUC of the NRS-A score through 24 hours (NRS-A0-24; primary endpoint) was showed compared with saline placebo (primary analysis).

It is expected that a product containing a high-dose bupivacaine shows some activity compared to placebo but these exploratory results are not considered sufficient for supporting an indication in mammoplasty.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development of Zynrelef (HTX-011) is based on two phase 3, randomized, double-blind, multicenter, active and placebo-controlled, pivotal studies (study 301 in bunionectomy and study 302 in herniorrhaphy). Overall, the design of these both Phase 3 was adequate.

The selection criteria were globally consistent with the target population for each surgical model.

Two doses of the fixed dose combination product were tested in phase 3 studies: bupivacaine 60 mg/ meloxicam 1.8 mg in bunionectomy and bupivacaine 300 mg/ meloxicam 9 mg in herniorrhaphy.

These doses and the administration technique were selected based on previous results on phase 2 studies (study 208 in bunionectomy and study 202 in herniorrhaphy). The dose to be applied depends upon the size of the surgical site and the volume required to coat the affected tissues.

The clinical development program involved two other phase 2 studies in total knee arthroplasty (TKA) and augmentation mammoplasty (study 209 and study 211 respectively). A higher dose of bupivacaine 400 mg/ meloxicam 12 mg was selected in these studies through increasing dose and administration techniques finding cohorts.

These surgical models have been selected to provide efficacy data of Zynrelef in bony and soft tissue surgical models with different pain levels, in different anatomic spaces with different vascularities and to support a broad indication in postoperative pain for 72 hours.

The active comparator selected for the clinical development was bupivacaine HCl administered as a single dose via injection into the surgical site. Bupivacaine solution for injection is at present the most appropriate active comparator as it is standard of care. However, most of its analgesic benefit occurred in the first 8 to 12 hours.

The primary endpoint and the key secondary endpoints were identical in both phase 3 studies. The mean AUC of the Numeric Rating Scale with activity (NRS-A) pain intensity scores through 72 hours (AUC0-72) for HTX-011 compared with saline placebo and compared with bupivacaine HCl, were primary and first key secondary endpoints respectively. According to CHMP Scientific Advice, the primary endpoint was only partially endorsed. The CHMP Scientific Advice highlight the fact that "[…] *it should be discussed and justified in advance which difference can be regarded clinically relevant for comparing the mean AUC0-72h of pain intensities. Statistical significance only does not suffice to demonstrate a clinically relevant effect. It is furthermore expected that the complete course of pain intensities over the measurement interval is presented. Taking into consideration the lack of an appropriate comparator with longer duration of effect an earlier time point will also be critical for assessment of efficacy and would usefully be included as co-primary EP, e.g. at least non-inferiority (which of course would not help to justify the addition of the meloxicam component of the combination) and preferably superiority on AUC0-6h when selecting bupivacaine solution for injection or HTX-002 as active comparator. AUC0-72h could*

then demonstrate the additional benefit of the new formulation". This advice was not fully followed by the applicant.

The clinically relevant difference for comparing the mean AUC0-72h of pain intensities has not been justified. As a consequence, clinical translation of obtained results in AUC are difficult to extrapolate and are open to interpretation.

The other key secondary endpoints are thus considered as important to appreciate clinical significance. There were mainly focused on opioids consumption (mean total postoperative opioid consumption through 72 hours and proportion of subjects who are opioid-free through 72 hours compared with saline placebo and bupivacaine HCl). This approach is endorsed as the recognized advantages of multimodal analgesia include improved analgesia, reduced opioids requirements and reduced adverse effects of opioids. However, it should be noted that "patient controlled analgesia" (PCA) appears to be the method of choice to estimate opioid sparing effect because an accurate measure of postoperative opioids needs should be preferably based on a method where patients can "freely" access opioids to relieve pain and accept some degree of undesirable effects. This method was not used to assess opioid sparing effect. Decreased opioid consumption is a legitimate important clinical objective considered that it is achieved through the same level of pain relief.

The choice of the time interval of 72 hours based on the assumption that most severe pain occurs within the first 72 hours after surgery is acceptable.

The primary and key secondary endpoints were different in TKA (mean AUC0-48 and AUC0-72 of NRS-R Pain Intensity Scores for HTX-011) and in augmentation mammoplasty (mean AUC0-24 of NRS-A pain intensity scores and mean total postoperative opioid consumption through 24, 48 and 72 hours) and considered only comparison with saline placebo. This was not considered optimal as Zynrelef is a fixed dose combination.

Efficacy data and additional analyses

Phase 3 studies in bunionectomy and herniorrhaphy

According to the primary analysis, Zynrelef (HTX-011), at the doses of bupivacaine 60 mg / meloxicam 1.8 mg and bupivacaine 300 mg/ meloxicam 9 mg, was superior to placebo and to bupivacaine HCl to manage postoperative pain in bunionectomy and herniorrhaphy (mean AUC0-72 of the NRS-A pain intensity scores using wWOCF in the defined ITT population). Sensitivity analysis (mean AUC0-72 of NRS-A pain intensity scores using LOCF/WOCF in the ITT population and mean AUC0-72 of NRS-A pain intensity scores using wWOCF in the per protocol population) were consistent with the primary analysis.

These results are in accordance with those observed on pain at rest compared with saline placebo (AUC0-72 of the NRS-R pain intensity scores using wWOCF in the defined ITT population).

These outcomes were supported by key secondary endpoints showing a reduced opioid consumption and higher proportion of opioid-free subjects over 72 hours.

The proportion of subjects with severe pain (≥7/10) was significantly reduced in HTX-011 group compared with saline placebo and bupivacaine HCl based on NRS-A (wWOCF, ITT population).

The clinically relevant difference for comparing the mean AUC0-72h of pain intensities has not been justified. As a consequence, clinical translation of obtained results in AUC are difficult to extrapolate and are open to interpretation. In study 301 in bunionectomy, the differences on mean AUC48-72 of the NRS-A and NRS-R pain intensity using wWOCF on the ITT population score between HTX-011 and bupivacaine HCl are not statistically significant. The difference on mean AUC0-72 of the NRS-R pain intensity using LOCF/WOCF on the ITT population score between HTX-011 and bupivacaine HCl is not

statistically significant. In study 302 in herniorrhaphy, there was no statistically significant difference between HTX-011 and saline placebo group after 48 hours post-dose (AUC48-72) on NRS-A of the pain intensity scores using wWOCF in the defined ITT population. There was no statistically significant difference between HTX-011 and both control groups after 48 hours (mean AUC48-72 of NRS-R pain intensity scores using wWOCF on the ITT population). Regarding mean AUCs of NRS-R pain intensity scores over time analyzed using LOCF/WOCF, there was no statistically significant difference between HTX-011 and both control groups after 24 hours (AUC24-48 and AUC48-72). There was also no statistically significant difference between HTX-011 and both control groups on the overall interval (AUC0-72).

Overall, phase 3 studies (301 and 302) showed positive results in favour of HTX-011 based on primary and key secondary endpoints. However, it remains a reasonable doubt that the effect size on the overall interval (AUC 0-72 hours) may be mainly driven by the effect size on the first day post-dose (AUC 0-24 hours) as well as that the opioid sparing effect on the overall interval (0-72 hours) may be mainly driven by the opioid sparing effect on the first day post-dose (0-24 hours). However, it is estimated that Zynrelef has a clinically significant effect on reduction of pain scores at least during the first 24 hours post-dose and the applicant successfully justified an opioid sparing effect associated with a decrease in ORAE in bunionectomy and herniorrhaphy. This opioid sparing effect of Zynrelef is considered as modest but clinically significant.

Phase 2 studies in total knee arthroplasty (TKA) and augmentation mammoplasty

According to the primary analysis, Zynrelef (HTX-011), at the doses of bupivacaine 400 mg / meloxicam 12 mg was superior to placebo in TKA and augmentation mammoplasty models.

In study 209 in TKA, ZYNRELF (HTX-011) bupivacaine 400 mg / meloxicam 12 mg was superior to placebo (mean AUC of NRS-R pain intensity scores using wWOCF in the defined ITT population) over 48 hours (primary endpoint) and over 72 hours (key secondary endpoint) compared with saline placebo. These results are in accordance with those observed on pain with activity compared with saline placebo. HTX-011 significantly reduced mean AUC of NRS-A pain intensity scores (wWOCF, ITT Population) on every time intervals compared to saline placebo (AUC0-24, AUC0-48 and AUC0-72). However, questions were raised as, according to the selected criteria, over a 72 hours period, HTX-011 bupivacaine 400 mg / meloxicam 12 mg does not provide a significant better analgesia than bupivacaine HCl (mean AUC of NRS-R pain intensity scores over time). The reduction of pain scores after 24 hours post-dose in HTX-011 group compared to saline placebo and bupivacaine seems limited. Overall, pain remains severe (≥7/10) in all treatment groups. The opioid sparing effect of HTX-011 seems limited in this surgical model and was not associated with a difference in proportion of subjects having used opioids and/or with a decrease in prespecified ORAEs. No significant sparing effect of HTX-011 compared to bupivacaine HCl could be highlighted.

It is estimated that phase 3 confirmatory results, including comparison of mean AUC0-72 of pain intensity scores between Zynrelef and bupivacaine HCl as a primary or first key secondary endpoint, would be necessary to include total knee arthroplasty as a therapeutic indication of Zynrelef.

Indeed, in TKA study, the primary and key secondary endpoint only considered a comparison against placebo and was not intended, nor powered, to demonstrate superiority to bupivacaine HCl. This is not considered sufficient for the following reasons:

- The criteria of AUC of pain intensity scores has no direct clinical translation and the minimum difference that would be considered as clinically significant when comparing AUC has not been justified.

- The small opioid sparing effect was not associated with a decrease in prespecified ORAEs and is not considered as clinically significant.

Augmentation mammoplasty study (211) was an exploratory study where reduction in mean AUC of the NRS-A score through 24 hours (NRS-A0-24; primary endpoint) was showed for HTX-011 administered via instillation (and via nerve block) compared with saline placebo. However, even if the study was not designed for this purpose, according to the applicant, compared with bupivacaine HCl via NB, both HTX-011 400 mg/12 mg treatment groups had lower mean AUC0-24 of the NRS-A pain-intensity scores but these differences were not statistically significant. After 24 hours post-dose, there is no clinically meaningful difference in pain scores between HTX-011 400 mg/12 mg and both control groups. Mean and median total opioid consumption in MME over 72 hours were numerically higher in HTX-011 400 mg/12 mg administered via instillation compared to both control groups. These results are not sufficient to assess the B/R in augmentation mammoplasty.

Broad indication in postoperative pain

Justification for a broad indication and posology cannot be based on regulatory precedence to already approved local anaesthetics. Claimed indication should only be based on evidence from the development programme.

Considering the efficacy of the new product in treatment of acute pain, the Guideline on the Clinical Development of Medicinal Products Intended for the Treatment of Pain states, that "*The efficacy profile of a new product should normally be established in separate studies for both somatic and visceral nociceptive pain*" and "*to justify a general indication for the treatment of acute pain, efficacy needs to be demonstrated independently in models of both somatic and visceral pain, or in models of somatic pain and mixed somatic/visceral pain*". In the case of HTX-011 the studied models represent moderate to severe somatic pain model (Bunionectomy study 301, 208; Total knee arthroplasty study 209) and mixed somatic/visceral mild to moderate pain (Herniorrhaphy study 302, 202 and supportive study in augmentation mammoplasty). There was no data provided on the analgaesic effect of HTX-011 in visceral moderate to severe pain models or mixed somatic/visceral moderate to severe pain models, which represents major abdominal, thoracic or vascular surgeries. The applicant's argument to replace missing pain models with the mechanism of action of the fixed combination is not endorsed as justification is only based on an assumption.

While evidence of efficacy can be extrapolated to less severe pain categories within the same model, in this case, the applicant did not provide evidence of efficacy in moderate to severe somatic/visceral pain models or visceral moderate to severe pain models. Although the applicant stated during the evaluation that HTX 011 is intended to treat somatic postoperative soft tissue and bony pain, not visceral pain, the proposed indication was not limited to surgeries representing only somatic pain. The applicant also accepted the deletion of the mention "for up to 72 hours" from the therapeutic indication and proposed the addition of the adjective "somatic" to the indication wording. The final indication was agreed to be: Zynrelef is indicated for treatment of somatic postoperative pain from small- to medium-sized surgical wounds in adults (see section 5.1).

Uncertainties remain on the clinical significance of the effect in tested surgeries because the primary endpoint of phase 3 studies is only partially endorsed in line with the scientific advice and the minimum difference that would be considered as clinically significant when comparing AUC of pain intensity scores has not been justified. It should be moreover considered that intrinsic factors with incidence on pain management should be considered across different types of surgery.

It is estimated that phase 3 confirmatory results, including comparison of mean AUC0-72 of pain intensity scores between Zynrelef and bupivacaine HCl as a primary or first key secondary endpoint, will be

necessary to include total knee arthroplasty as a therapeutic indication of Zynrelef. Indeed, in TKA study, the primary and key secondary endpoint only considered a comparison against placebo. Augmentation mammoplasty study (211) was an exploratory study where reduction in mean AUC of the NRS-A score through 24 hours (NRS-A0-24; primary endpoint) was showed but does not provide sufficient results to assess the B/R in this surgery.

The proposed posology was also questioned regarding a broad indication in postoperative pain. The current proposed Zynrelef's administration is limited to a 14 mL volume corresponding to the maximum total dose (about 400 mg / 12 mg). It is not known if this volume will be sufficient to coat the affected tissues within others surgical sites that could result in pain generation. Conversely, in case of mini-invasive surgery with very small incision, the use of a small volume of Zynrelef in the wound might be inefficient: Zynrelef is provided in a single concentration solution of 29.25 mg of bupivacaine and 0.88 mg of meloxicam per mL. During bunionectomy study (301), the use of the defined volume of 2.1 mL was associated with difficulty in suturing some patients with leaks of product. Moreover, this surgery is already at risk of impaired wound healing and dehiscence. The physical presence of a viscous solution (Zynrelef) in the wound has been associated with a slight increase of this risk in the study. It could then be questioned how to assess these specific surgery type risks that likely exist in other surgeries.

It is endorsed that surgeons routinely determine the dosing requirements for different surgical wounds, based on the maximum allowable dose and that it would be impossible to provide dosing recommendations for each procedure. Still, from the CHMP's opinion, there is some difference between a local injection of bupivacaine and an instillation of Zynrelef. Indeed, when Zynrelef has been administered and surgical wound has been closed, there is no adapting possibility whereas it is possible to inject a second dose of bupivacaine while not exceeding the maximum recommended dose.

As a consequence, it was estimated that Zynrelef recommended posology has to be more strictly defined in the SmPC, for efficacy as well as for safety reasons. The applicant was asked to define a range of volume with a reasonable presumption of efficacy/safety (X to Y mL). The applicant justified that a range of doses cannot be determined based on the data from clinical studies. Instructions regarding the use of adequate amount is proposed by the applicant associated with a warning to avoid excess use that could be deleterious for the site closure. Even not entirely satisfactory, the applicant's proposal is considered acceptable.

Fixed dose combination considerations

The CHMP considered that based on general methodological principles, in order to establish the efficacy and safety of each component of the fixed dose combination, an appropriate phase III design would have been a randomized three-arm study of bupivacaine + meloxicam versus bupivacaine and versus meloxicam. However, despite the fact that such study has not been submitted by the applicant, the efficacy of bupivacaine in the combination can be considered established on the basis of the overall clinical results as well as known efficacy profile of this active substance. Concerning meloxicam, although conclusive clinical trials investigating its activity in the combination in the claimed indication are lacking, the inference of the contribution to efficacy can be considered sufficiently established based on biological and pharmacological rationale, as well as relevant non-clinical and clinical data, most notably from Phase 2 studies. These studies utilised investigational, prolonged-release bupivacaine-only and meloxicam-only comparator formulations prepared in the same polymer as Zynrelef to assess the contribution of each active ingredient to the combination product. The efficacy of Zynrelef was superior to that of prolonged-release bupivacaine alone, at the same bupivacaine dose, in both study 202 and study 208.

2.5.4. Conclusions on the clinical efficacy

Studied models in Zynrelef's development programme represent moderate to severe somatic pain model (Bunionectomy study 301, 208; Total knee arthroplasty study 209) and mixed somatic/visceral mild to moderate pain (Herniorrhaphy study 302, 202 and supportive study in Augmentation mammoplasty). There is no provided data on the analgesic effect of HTX-011 in visceral moderate to severe pain models or mixed somatic/visceral moderate to severe pain models, which represents major abdominal, thoracic or vascular surgeries. The applicant's argument to replace missing pain models with the mechanism of action of the fixed combination is not endorsed as justification is only based on an assumption.

Considering the efficacy of the new product in treatment of acute pain, the Guideline on the Clinical Development of Medicinal Products Intended for the Treatment of Pain states, that "The efficacy profile of a new product should normally be established in separate studies for both somatic and visceral nociceptive pain" and "to justify a general indication for the treatment of acute pain, efficacy needs to be demonstrated independently in models of both somatic and visceral pain, or in models of somatic pain and mixed somatic/visceral pain". Therefore, based on the clinical efficacy data provided by the applicant, a broad indication is not justified.

It also remains uncertainties on the clinical significance of the effect in tested surgeries because the primary endpoint of phase 3 studies is only partially endorsed in line with the scientific advice and the minimum difference that would be considered as clinically significant when comparing AUC of pain intensity scores has not been justified. It should be moreover considered that intrinsic factors with incidence on pain management should be considered across different types of surgery.

More precisely, in studies 301 and 302, it could not be excluded that the effect size on pain (AUC of NRS scores) and decreased opioid consumption on the overall interval (0-72 hours) may be mainly driven by the effects size on the first day post-dose (0-24 hours). However, it is estimated that Zynrelef has a clinically significant effect on reduction of pain scores during at least the first 24 hours post-dose and the applicant successfully justified an opioid sparing effect associated with a decrease in ORAE in bunionectomy and herniorrhaphy. The opioid sparing effect of Zynrelef in these two surgical models is considered as modest but clinically significant.

Nevertheless, further evidence of efficacy for other tested models are lacking and cannot be also extrapolated.

2.6. Clinical safety

The safety data included in the analysis are from 8 studies that evaluated the intended commercial formulation: one Phase 1, three Phase 2a, two Phase 2b and two Phase 3.

In the Phase 3 studies, HTX-011 was evaluated at dose levels of 60 mg/1.8 mg or 300 mg/9 mg administered by instillation into the surgical site. The focus of the integrated analysis of safety is on the pooled data from two Phase 3 studies (in bunionectomy or herniorrhaphy) and two Phase 2b studies (in TKA or mammoplasty), which only evaluated HTX-011, the intended commercial formulation. Because the intended administration technique for HTX-011 is instillation, only data for HTX-011 administered by instillation are included in the pooled dataset.

Additional supportive safety data are from one Phase 1 study (in healthy volunteers) and three Phase 2a studies (in herniorrhaphy, mini- or complete abdominoplasty, or bunionectomy).

These were not pooled with those from the Phase 3 and Phase 2b studies because of the following reasons:

- They were exploratory formulation-, dose-, and administration technique-finding studies;

- Safety assessment measures and timepoints were different from those in Phase 3 and Phase 2b studies;
- Small numbers of subjects were administered HTX-011 by instillation and at dose levels common to the Phase 3 and Phase 2b studies.

Overall, studies were conducted in 5 unique surgical procedures (2 different bony models and 3 different soft tissue models) with different anatomic spaces, vascularities, and levels of pain in diverse patient populations, across various populations receiving, for the large majority of the, pain medication (opioids and non-opioids "on demand" with specific dose regimen for each subject) and with 4 different doses of HTX-011 (ranging from 60mg/1.8mg (bupivacaine meloxicam) to 400mg/12mg). Considering these specificities, the proposed pooling approach is too limited and does not allow to assess precisely HTX-011 safety profile. For safety concerns requiring a specific attention (i.e. local treatment adverse events (TEAEs), LAST-related TEAEs), safety data detailed in each individual clinical study report will be presented.

Patient exposure

Exposure in Phase 2b and Phase 3 Studies

The patient exposure in pooled clinical trials in Phase 2b and 3 studies is summarised in the Table below.

Table 45: Treatment groups in pooled analysis of safety of HTX-011.

Treatment	Dose Level	N	Study (Surgical Procedure)
HTX-011 via instillation	60 mg/1.8 mg	157	301 (bunionectomy)
	200 mg/6 mg	20	209 (TKA)
	300 mg/9 mg	163	302 (herniorrhaphy)
	400 mg/12 mg	164	209 (TKA), 211 (bilateral augmentation mammoplasty)[a]
	Total number of subjects administered HTX-011: 504		
Bupivacaine HCl via injection	50 mg	154	301 (bunionectomy)
	75 mg	173	302 (herniorrhaphy)
	125 mg	65	209 (TKA)
	Total number of subjects administered bupivacaine HCl: 392		
Saline placebo via instillation or injection	Not applicable	247	209 (TKA), 301 (bunionectomy), and 302 (herniorrhaphy)
	Total number of subjects administered saline placebo: 247		

Abbreviations: TKA, total knee arthroplasty.
Note: HTX-011 (also referred to as HTX-011-56) is the intended commercial formulation and was the only formulation evaluated in the Phase 3 and Phase 2b studies.
[a] In Study 211, HTX-011 was administered via instillation into the intended space for each implant, 200 mg/6 mg per side for a total dose of 400 mg/12 mg.

Exposure in Phase 1 and Phase 2a Studies

In the Phase 1 study, only the intended commercial formulation was evaluated. In Phase 2a studies, earlier formulations and/or formulations containing only bupivacaine and meloxicam were also evaluated. The results for these formulations and saline placebo used as a comparator for these formulations are not included in the analysis of safety of HTX-011.

Maximum HTX-011 dose exposure

A large number of subjects have been exposed to the proposed maximum recommended dose of 400 mg/12 mg: a total of 364 subjects undergoing various surgical procedures received the 400 mg/12 mg dose in clinical studies, including 202 subjects who received this dose via instillation only and 90 additional subjects who received this dose via a combination of instillation and injection.

Demographic and disease characteristics

- *Phase 3 and Phase 2b Studies*

In Phase 3 and 2b studies, the demographics and baseline characteristics were generally well balanced for saline placebo, total bupivacaine HCl, and total HTX-011. Approximately half of the subjects were males (ranging from 47.2% to 54.3%) and half females (ranging from 45.7% to 52.8%). The mean age of the subjects ranged from 50.0 to 51.3 years. The proportion of subjects ≥65 years old was higher for total HTX-011 (19.0%) than for saline placebo (14.5%) and total bupivacaine HCl (12.8%). The race of the majority of the subjects was White.

- *Phase 1 and Phase 2a Studies*

The demographic and baseline characteristics were generally similar between HTX-011, bupivacaine HCl and placebo groups in each study. Some differences between the pooled characteristics for HTX-011 groups and specific surgery could be noted:

- in study 211, the mean age was low (32 years old) compared to mean age in all HTX-011 groups (32 vs. 46.9 years old) as well as BMI (24 vs. 27.65 kg/m^2);
- in 209 and 208 (HTX-011 120mg/3.6mg arm) the mean BMI is higher compared to mean BMI in all HTX-011 groups (respectively >31 and >30 kg/m^2 (obesity));
- in study 208 (HTX-011 60mg/1.8mg arm) the mean BMI of HTX-011 group is lower than bupivacaine and placebo groups (respectively 27.6 vs 31.75 and 30.26 kg/m^2);
- in the HTX-011 groups, in study 203 female and in study 202 male were predominantly enrolled (99%).

Adverse events

Overview of adverse events

Phase 3 and Phase 2b Studies

In Phase 3 and 2b studies, the incidences of any TEAE were similar for total HTX-011, pooled saline placebo, and total bupivacaine HCl, and ranged from 81.4% to 84.1%. The majority of TEAEs were mild or moderate in severity. The incidence of severe TEAEs was low and similar for total HTX-011, pooled saline placebo, and total bupivacaine HCl and ranged from 2.4% to 3.2%. The incidence of severe TEAEs did not increase with increasing doses of HTX-011. The incidence of SAEs was low and similar for total

HTX-011, pooled saline placebo, and total bupivacaine HCl, and ranged from 1.8% to 2.2%. The incidence was slightly higher for HTX-011 400 mg/12 mg (3.7%) and bupivacaine HCl 125 mg (4.6%) compared with pooled saline placebo (2.0%) and other dose levels of HTX-011 or bupivacaine HCl (ranging from 0% to 1.9%).

Phase 1 and Phase 2a Studies

In study 202, for HTX-011 (all doses and administration techniques pooled), the incidence of any TEAE was 73.3% (96 of 131 subjects). Incidences were 65.9% (56 of 85 subjects) for saline placebo and 65.5% (21 of 32 subjects) for bupivacaine HCl 75 mg. The incidence of TEAEs did not increase with increasing doses of HTX-011. The majority of TEAEs were mild or moderate in severity. The incidence of SAEs was lower for HTX-011 (all doses and administration techniques pooled) compared with saline placebo or bupivacaine HCl 75 mg. There were no TEAEs that led to withdrawal from the study. Among subjects administered HTX-011 300 mg/9 mg, 50.0% (8 of 16 subjects) experienced a study drug-related TEAE. Incidences of study drug-related TEAEs for saline placebo and bupivacaine HCl 75 mg were 28.2% (24 of 85 subjects) and 28.1% (9 of 32 subjects), respectively.

In Study 203 (*complete abdominoplasty*), HTX-011 was administered as follows: 300 mg/9 mg by combination; or 400 mg/12 mg by instillation or combination. The results presented in this section for HTX-011 400 mg/12 mg are pooled across administration techniques. Incidences of any TEAE were similar for HTX-011 (all doses and administration techniques pooled) (89.6%; 69 of 77 subjects), saline placebo (87.5%; 28 of 32 subjects), and bupivacaine HCl 100 mg (88.2%; 15 of 17 subjects). It did not increase with increasing doses of HTX-011. The majority of TEAEs were mild or moderate in severity. Two subjects experienced an SAE: 1 of 17 (5.9%) administered bupivacaine HCl 100 mg and 1 of 35 (2.9%) administered HTX-011 300 mg/9 mg. There were no TEAEs that led to withdrawal from the study.

In Study 208, HTX-011 was administered as follows: 30 mg/0.9 mg by injection using a Mayo block; 60 mg/1.8 mg by injection, injection using a Mayo block, or instillation with a Luer lock applicator; 120 mg/3.6 mg by injection, injection using a Mayo block, instillation, or instillation with a Luer lock applicator; or 200 mg/6 mg by injection or injection using a Mayo block. The results presented are pooled across administration techniques for each dose level (except for HTX-011 30 mg/0.9 mg). The incidence of any TEAE for HTX-011 (all doses and administration techniques pooled) (72.4%; 126 of 174 subjects) was similar to that for saline placebo (73.1%; 76 of 104 subjects) and lower than that for bupivacaine HCl 50 mg (80.0%; 20 of 25 subjects). Incidences of TEAEs did not increase with increasing doses of HTX-011. The majority of TEAEs were mild or moderate in severity. One of 30 (3.3%) subjects administered HTX-011 200 mg/6 mg experienced an SAE. One of 104 (1.0%) subjects administered saline placebo experienced a TEAE that led to withdrawal from the study.

The incidence of any TEAE was lower for HTX-011 60 mg/1.8 mg (63.5%; 33 of 52 subjects) compared with saline placebo (73.1%; 76 of 104 subjects) and bupivacaine HCl 50 mg (80.0%; 20 of 25 subjects). Similarly, the incidence of study drug-related TEAEs was also lower for HTX-011 60 mg/1.8 mg (19.2%; 10 of 52 subjects) compared with saline placebo (24.0%; 25 of 104 subjects) and bupivacaine HCl 50 mg (28.0%; 7 of 25 subjects).

In Study 102 in healthy volunteers, subjects were administered HTX-011 400 mg/12 mg SC divided into 16 total injections. All subjects experienced at least 1 TEAE and at least 1 study drug-related TEAE. All TEAEs were mild or moderate in severity. There were no SAEs.

In a general way, the incidence and severity of TEAEs and the incidence of SAEs reported across placebo, bupivacaine HCl and HTX-011 groups is quite similar, except for local TEAEs. In study 301, the incidence of local inflammatory TEAEs is higher was HTX-011 60mg/1.8mg than placebo and 50mg bupivacaine

HCl groups (respectively 28.7%, 19.8% and 22.1%). The incidence of local TEAEs seems not increase with increasing doses of HTX-011.

Most common adverse events

Overview of most reported adverse events Phase 3 and Phase 2b Studies

The TEAEs by PT with an incidence of ≥5% for pooled saline placebo or any dose level of HTX-011 or bupivacaine HCl in the Phase 3 and Phase 2b studies are presented in Table 41 and Table 42.

For HTX-011 200 mg/6 mg, the number of subjects was small, which limits interpretation of the results for this dose.

Table 46: Incidence of the Most Common TEAEs by Preferred Term in Phase 3 and Phase 2b Studies

Preferred Term n (%)	Saline Placebo (N = 247)	Bupivacaine HCl				HTX-011				
		50 mg (N = 154)	75 mg (N = 173)	125 mg (N = 65)	Total (N = 392)	60 mg/1.8 mg (N = 157)	200 mg/6 mg (N = 20)	300 mg/9 mg (N = 163)	400 mg/12 mg (N = 164)	Total (N = 504)
Any TEAE	201 (81.4%)	131 (85.1%)	127 (73.4%)	61 (93.8%)	319 (81.4%)	131 (83.4%)	19 (95.0%)	119 (73.0%)	155 (94.5%)	425 (84.1%)
Nausea	103 (41.7%)	70 (45.5%)	37 (21.4%)	34 (52.3%)	141 (36.0%)	59 (37.6%)	14 (70.0%)	30 (18.4%)	96 (58.5%)	199 (39.5%)
Constipation	36 (14.6%)	18 (11.7%)	41 (23.7%)	21 (32.3%)	80 (20.4%)	9 (5.7%)	8 (40.0%)	28 (17.2%)	42 (25.6%)	87 (17.3%)
Dizziness	44 (17.8%)	36 (23.4%)	42 (24.3%)	11 (16.9%)	89 (22.7%)	34 (21.7%)	5 (25.0%)	24 (14.7%)	23 (14.0%)	86 (17.1%)
Vomiting	37 (15.0%)	33 (21.4%)	12 (6.9%)	17 (26.2%)	62 (15.8%)	23 (14.6%)	7 (35.0%)	7 (4.3%)	48 (29.3%)	85 (16.9%)
Headache	22 (8.9%)	20 (13.0%)	24 (13.9%)	5 (7.7%)	49 (12.5%)	22 (14.0%)	3 (15.0%)	21 (12.9%)	13 (7.9%)	59 (11.7%)
Tachycardia	13 (5.3%)	0	4 (2.3%)	6 (9.2%)	10 (2.6%)	1 (0.6%)	4 (20.0%)	4 (2.5%)	24 (14.6%)	33 (6.5%)
Bradycardia	12 (4.9%)	12 (7.8%)	16 (9.2%)	1 (1.5%)	29 (7.4%)	12 (7.6%)	0	15 (9.2%)	3 (1.8%)	30 (6.0%)
Pyrexia	8 (3.2%)	1 (0.6%)	3 (1.7%)	10 (15.4%)	14 (3.6%)	2 (1.3%)	1 (5.0%)	5 (3.1%)	22 (13.4%)	30 (6.0%)
Incision site oedema	14 (5.7%)	22 (14.3%)	0	0	22 (5.6%)	27 (17.2%)	0	0	0	27 (5.4%)
Hypotension	8 (3.2%)	7 (4.5%)	7 (4.0%)	1 (1.5%)	15 (3.8%)	7 (4.5%)	0	7 (4.3%)	11 (6.7%)	25 (5.0%)
Hypertension	15 (6.1%)	1 (0.6%)	2 (1.2%)	11 (16.9%)	14 (3.6%)	0	2 (10.0%)	2 (1.2%)	19 (11.6%)	23 (4.6%)
Incision site erythema	11 (4.5%)	18 (11.7%)	4 (2.3%)	0	22 (5.6%)	20 (12.7%)	0	0	3 (1.8%)	23 (4.6%)
Pruritus	7 (2.8%)	1 (0.6%)	3 (1.7%)	5 (7.7%)	9 (2.3%)	8 (5.1%)	2 (10.0%)	0	12 (7.3%)	22 (4.4%)
Dysgeusia	10 (4.0%)	6 (3.9%)	21 (12.1%)	0	27 (6.9%)	4 (2.5%)	0	15 (9.2%)	2 (1.2%)	21 (4.2%)
Post procedural contusion	13 (5.3%)	18 (11.7%)	0	0	18 (4.6%)	19 (12.1%)	0	0	0	19 (3.8%)
Muscle twitching	9 (3.6%)	8 (5.2%)	6 (3.5%)	0	14 (3.6%)	9 (5.7%)	0	6 (3.7%)	1 (0.6%)	16 (3.2%)
Pruritus generalised	11 (4.5%)	8 (5.2%)	1 (0.6%)	2 (3.1%)	11 (2.8%)	4 (2.5%)	2 (10.0%)	2 (1.2%)	8 (4.9%)	16 (3.2%)
Hyperhidrosis	4 (1.6%)	2 (1.3%)	0	0	2 (0.5%)	3 (1.9%)	4 (20.0%)	0	7 (4.3%)	14 (2.8%)
Leukocytosis	2 (0.8%)	3 (1.9%)	0	2 (3.1%)	5 (1.3%)	1 (0.6%)	1 (5.0%)	0	11 (6.7%)	13 (2.6%)

Muscle spasms	11 (4.5%)	1 (0.6%)	1 (0.6%)	5 (7.7%)	7 (1.8%)	0	3 (15.0%)	0	10 (6.1%)	13 (2.6%)
Skin odour abnormal	1 (0.4%)	0	1 (0.6%)	0	1 (0.3%)	0	0	13 (8.0%)	0	13 (2.6%)
Hypokalaemia	7 (2.8%)	0	1 (0.6%)	7 (10.8%)	8 (2.0%)	1 (0.6%)	2 (10.0%)	0	9 (5.5%)	12 (2.4%)
Impaired healing	1 (0.4%)	6 (3.9%)	0	0	6 (1.5%)	10 (6.4%)	0	0	0	10 (2.0%)
Medical device site reaction	3 (1.2%)	1 (0.6%)	1 (0.6%)	3 (4.6%)	5 (1.3%)	0	0	0	10 (6.1%)	10 (2.0%)
Urinary retention	8 (3.2%)	0	3 (1.7%)	2 (3.1%)	5 (1.3%)	0	0	1 (0.6%)	9 (5.5%)	10 (2.0%)
Sinus arrhythmia	6 (2.4%)	10 (6.5%)	3 (1.7%)	0	13 (3.3%)	6 (3.8%)	0	3 (1.8%)	0	9 (1.8%)
Tremor	11 (4.5%)	2 (1.3%)	12 (6.9%)	1 (1.5%)	15 (3.8%)	0	0	7 (4.3%)	2 (1.2%)	9 (1.8%)
Tinnitus	7 (2.8%)	8 (5.2%)	6 (3.5%)	1 (1.5%)	15 (3.8%)	2 (1.3%)	0	3 (1.8%)	2 (1.2%)	7 (1.4%)
Anaemia postoperative	7 (2.8%)	0	0	2 (3.1%)	2 (0.5%)	0	4 (20.0%)	0	2 (1.2%)	6 (1.2%)
Oedema peripheral	3 (1.2%)	0	0	2 (3.1%)	2 (0.5%)	2 (1.3%)	2 (10.0%)	0	1 (0.6%)	5 (1.0%)
Dry mouth	1 (0.4%)	0	1 (0.6%)	2 (3.1%)	3 (0.8%)	0	3 (15.0%)	0	0	3 (0.6%)
Hyponatraemia	3 (1.2%)	0	0	4 (6.2%)	4 (1.0%)	0	1 (5.0%)	0	1 (0.6%)	2 (0.4%)
Pain	2 (0.8%)	0	0	0	0	0	2 (10.0%)	0	0	2 (0.4%)

Abbreviation: TEAE, treatment-emergent adverse event.
Notes: the TEAEs with an incidence of ≥5% for saline placebo or any dose level of bupivacaine HCl or HTX-011 are presented. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.1. For each Preferred Term (PT), subjects are included only once, even if they experienced multiple events in that PT. TEAEs are presented in descending order of frequency in the total HTX-011 group.
Bupivacaine HCl 50 mg and HTX-011 60 mg/1.8 mg were used in Study 301 (bunionectomy).
Bupivacaine HCL 75 mg and HTX-011 300 mg/9 mg were used in Study 302 (herniorrhaphy).
Bupivacaine HCL 125 mg and HTX-011 200 mg/6 mg and 400 mg/12 mg were used in Study 209 (total knee arthroplasty).
HTX-011 400 mg/12 mg was used in Study 211 (mammoplasty). In Study 211, 200 mg/6 mg of HTX-011 was administered into each incision.
Source: Module 5, Section 5.3.5.3, ISS Table 2.2.8.

Table 47: Incidence of the most common TEAEs in studies 209 and 211.

Preferred Term n (%)	Study 209, Cohort 2			Study 211	
	Saline Placebo (N = 53)	Bupivacaine HCl 125 mg (N = 55)	HTX-011 400 mg/12 mg (N = 114)	Saline Placebo via Nerve Block (N = 41)	HTX-011 400 mg/12 mg
Any TEAE	50 (94.3%)	51 (92.7%)	107 (93.8%)	36 (87.8%)	48 (96.0%)
Nausea	25 (47.2%)	30 (54.5%)	59 (51.7%)	26 (63.4%)	37 (74.0%)
Constipation	12 (22.6%)	18 (32.7%)	35 (30.7%)	8 (19.5%)	7 (14.0%)
Vomiting	10 (18.9%)	15 (27.3%)	29 (25.4%)	16 (39.0%)	19 (38.0%)
Tachycardia	11 (20.8%)	6 (10.9%)	18 (15.8%)	2 (4.9%)	6 (12.0%)
Hypertension	8 (15.1%)	7 (12.7%)	19 (16.7%)	0	0
Leukocytosis	0	1 (1.8%)	10 (8.8%)	0	1 (2.0%)
Pyrexia	2 (3.8%)	8 (14.5%)	16 (14.0%)	0	6 (12.0%)

Abbreviation: TEAE, treatment-emergent adverse event.
Notes: TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.1. For each Preferred Term (PT), subjects are included only once, even if they experienced multiple events in that PT.
Source: Module 5, Section 5.3.5.1, Study 209 CSR, Table 39, Table 14.3.1.3.2; Study 211 CSR, Table 22, Table 14.3.1.3.

Overview of most reported adverse events Phase 2a and Phase 1 studies

In Study 202, the TEAEs with an incidence of >10% (more than 8 subjects) for HTX-011 400 mg/12 mg were nausea (27.7%; 23 of 83 subjects), constipation (24.1%; 20 of 83 subjects), and headache (20.5%; 17 of 82 subjects). These were also the most common TEAEs for saline placebo and bupivacaine HCl 75 mg. Their incidence did not increase with increasing doses of HTX-011. For HTX-011 300 mg/9 mg, constipation was the most common TEAE with the incidence of 37.5% (6 of 16 subjects). Nausea and headache were observed in 1 of 16 subjects (6.3%) administered HTX-011 300 mg/9 mg.

In Study 203 (*complete abdominoplasty*), the TEAEs observed in ≥5 subjects for HTX-011 400 mg/12 mg were nausea (61.9%; 26 of 42 subjects), constipation (28.6%; 12 of 42 subject), headache (19.0%; 8 of 42 subjects), pruritus (14.3%; 6 of 42 subjects), and tachycardia (11.9%; 5 of 42 subjects). Of these TEAEs, for saline placebo and bupivacaine HCl 100 mg, nausea, constipation, headache, pruritus,

and tachycardia (bupivacaine HCl 100 mg only) were among the most common TEAEs. There was no apparent dose-response in incidences of these TEAEs. Incidences of headache and pruritus were lower HTX-011 400 mg/12 mg compared with those for saline placebo. For bupivacaine HCl 100 mg, the incidence of nausea was higher than those for HTX-011 400 mg/12 mg and incidences of tachycardia and pruritus were similar to those for HTX-011 400 mg/12 mg.

In Study 208, the TEAEs observed in ≥5 subjects for HTX-011 60 mg/1.8 mg were nausea (30.8%; 16 of 52 subjects), vomiting (15.4%; 8 of 52 subjects), and headache (9.6%; 5 of 52 subjects). These were also common TEAEs for saline placebo and bupivacaine HCl 50 mg with incidences higher than those for HTX-011 60 mg/1.8 mg. With the exception of headache, the incidence of these TEAEs did not increase with increasing doses of HTX-011.

In Study 102 in healthy volunteers, the most frequent TEAEs (with an incidence ≥30%; 3 or more subjects) following SC administration of HTX-011 400 mg/12 mg were injection site bruising (80.0%; 8 of 10 subjects), injection site pain (60.0%; 6 of 10 subjects), injection site warmth (50.0%; 5 of 10 subjects), injection site erythema (40.0%; 4 of 10 subjects), injection site nodule (40.0%; 4 of 10 subjects), and injection site swelling (30.0%; 3 of 10 subjects). These TEAEs were attributed to SC route of administration of HTX-011; HTX-011 in this study was administered by 16 SC injections.

In general, no dose-dependent incidence in TEAEs onset was identified across the phase 3 and 2 studies, TEAEs onset seems to be specific to each dose and surgery. In Phase 3 and 2b studies, the most TEAEs reported in HTX-011 groups (more than 5% of all subjects receiving HTX-011) and with an slightly higher incidence than placebo are: constipation (17.3% in HTX-011 vs. 14.6% in placebo group), vomiting (16.9% vs. 15%), headache (11.7% vs. 8.9%), tachycardia (6.5% vs. 5.3%), bradycardia (6.0% vs.4.9%). This trend was also identified in Phase 2 studies, and subject local TEAEs were mostly reported in Phase 1 study in subject receiving HTX-011 in subcutaneous.

Opioid-Related Adverse Events (ORAEs)

For Phase 3, Phase 2b and Phase 2a Studies, ORAEs were pre-specified by the Sponsor as TEAEs that coded to any of the following PTs, regardless of whether subjects took opioid medication: *Nausea; Vomiting; Pruritus; Pruritus generalized (only for phase 3 and 2b studies); Respiratory depression; Urinary retention; Constipation* and *Somnolence*. Of note, in Study 209 in TKA and Study 211 in mammoplasty, only opioid rescue medication was available.

In general, subjects receiving HTX-011 in Phase 3 studies experienced less OREAs than placebo groups and bupivacaine HCl groups. This is consistent with the proportion of opioids-free subjects in these 2 studies (28.7% in 301 study and 51.5% in 302 study). "Nausea", "vomiting" and "constipation" are less or similarly reported in these studies in HTX groups than placebo and bupivacaine HCl groups.

Local Anesthetic Systemic Toxicity (LAST)

- *Potential LAST-related TEAEs*

In Phase 3 Studies 301 and 302 and Phase 2b Studies 209 and 211, symptoms that may be attributed to LAST were reviewed by searching the clinical database for PTs prespecified by the Sponsor based on the published literature (Vasques 2015). These selected PTs are: "Arrhythmia"; "Bradycardia"; "Cardiac arrest"; "Dizziness"; "Dysgeusia"; "Hypotension"; "Muscle twitching"; "Paraesthesia"; "Paraesthesia oral"; "Respiratory arrest"; "Seizure"; "Tinnitus"; "Tremor"; "Vision blurred"; "Visual impairment".

In studies 301 and 302, dizziness, bradycardia, hypotension, dysguesia, muscle twitching, were reported as more frequent in HTX-011 groups compared to the placebo group, but with a similar frequency than

the bupivacaine HCl control groups. The frequency of most of potential LAST-related TEAEs is, in most of cases, similar or higher in the HTX-011 low dose group (60mg/1.8mg) compared to the HTX-011 high dose groups (300mg/9mg and 400mg/12mg). Compared to the respective incidence of LAST-related AEs in the placebo groups for each study, no specific trend to an over-represented of these AEs with the 60mg/1.8mg HTX-011 dose is identified.

Taken individually, some of LAST-AEs are identified more frequently in HTX-011 groups than placebo and with a similar or higher frequency than bupivacaine groups (namely "hypotension", "bradycardia" and "tinnitus" in study 209 cohort 2; "hypotension" in study 211; "dizziness", "bradycardia", "hypotension" in study 301; "bradycardia", "dysgeusia", "paresthesia"/"paresthesia oral", "sinus arrhythmia", "vision blurred", in study 302). As mentioned by Vasques, MD et al.[1] (2015), "confusion, dizziness, tinnitus, dysgeusia, hallucinations, slurred speech, gait problems, limb twitching, extremity paresthesia, intention tremor, hypotonia, and facial sensorimotor and eye movement abnormalities [are minor central nervous system (CNS) abnormalities] and defined as prodromal manifestations of toxicity when they occurred either alone or before major signs of toxicity". The authors identified these prodromal signs as the most frequent CNS manifestations of LAST. Similarly, they identified hypotension and bradycardia as the most frequent signs of cardiovascular toxicity.

In 209 study, the potential LAST-related TEAEs identified in cohort 1 and cohort 2 were consistent with those identified in bupivacaine HCl 125mg and placebo groups (2 dizziness on each HTX-011 120mg/3.6mg and 60mg/1.8mg (by instillation) groups).

In the study 211, hypotension in the HTX-011 400mg/12mg via instillation is reported with a high incidence compared to the placebo and bupivacaine HCl 50mg groups (12% for HTX-011 group, vs. 2.4% for placebo and HCl groups). The applicant considers the AEs of hypotension retrieved in study 211 as non-LAST-related AEs because the bupivacaine plasma concentrations for these 6 subjects prior to the onset of the hypotension TEAE ranged from 118 to 632 ng/mL. Regarding the choice of the applicant to use the threshold plasma concentration of bupivacaine of 2,000 ng/mL as unique criteria to characterize an AE as LAST or not, this approach is questionable. Indeed, regarding this threshold, G.T. Tucker[2] (1986) specifies that "although these values are useful guidelines, they refer to the mythical "average subject" and must be interpreted in the light of a number of considerations (such as, total vs. free Concentrations; ionized vs. un-ionized)". Hasselstrom, M.D. et al.[3] (1984) reported a relevant case of patient experienced convulsions (serious LAST manifestation) for which the measured plasma concentration of bupivacaine was considered to be nontoxic (1,100ng/mL).

In Phase 2a Studies 202 and 203, the incidence of potential LAST-related TEAEs did not depend on the dose of HTX-011. Plasma concentrations of bupivacaine were not predictable of potential LAST-related TEAEs. The time of onset of potential LAST-related TEAEs did not correlate with maximal concentrations of bupivacaine.

In study 202, "Dizziness" and "hypotension" were more reported in HTX-011 300mg/9mg and 400mg/12mg groups than in HTX-011 200/6mg. "Muscle twitching" is more reported in HTX-011 200mg/9mg and HTX-011 400mg/12mg than in placebo group (respectively 3.1% and 3.6% vs. 0%) belong to possible symptom of bupivacaine-related CNS toxicity as mentioned in the current bupivacaine HCl SmPC. In 203 study, 5 subjects reported TEAEs potentially suggestive of LAST in the HTX-011 400mg/12mg group by instillation: 2 subjects experienced "dizziness", one subject

[1] Vasques F, Behr AU, Weinberg G, Ori C,Di Gregorio G. A Review of Local Anesthetic Systemic Toxicity Cases Since Publication of the American Society of Regional Anesthesia Recommendations: To Whom It May Concern. Regional Anesthesia and Pain Medicine 2015; 40(6): 698-705.
[2] Tucker GT. Pharmacokinetics of local anaesthetics. Br J Anaesth 1986; 58(7): 717-731.
[3] Hasselstrøm LJ, Mogensen T. Toxic reaction of bupivacaine at low plasma concentration. Anesthesiology. 1984;61:99–100.

"bradycardia", one subject "paresthesia" and one subject "tinnitus" (which belong to possible symptom of bupivacaine-related CNS toxicity).

- *Local Anesthetic Systemic Toxicity Assessment Questionnaire*

In Studies 301 and 302, a LAST assessment questionnaire was included to standardize the assessment process for identifying subjects who may experience signs or symptoms of LAST. Subjects were monitored for neurological and cardiac signs and symptoms potentially associated with LAST (e.g., *metallic/strange taste, perioral tingling, ringing in ears, visual disturbance, tremors, muscle twitching, dizziness/lightheadedness, convulsion/seizure, bradycardia, arrhythmia, hypotension, cardiac arrest, respiratory arrest*). Subjects were assessed with this questionnaire to identify early stages of toxicity to determine whether treatment of potential LAST-related signs or symptoms should be initiated (Table 48). Signs or symptoms that might be attributed to LAST were to be recorded as AEs and additional safety assessments were to be performed (vital sign measurements, 12-lead ECG, and blood sample collection to measure bupivacaine plasma concentrations). If symptoms were present at a timepoint when 1 of these assessments was not scheduled, an unscheduled assessment was performed.

Table 48: Summary of LAST assessment questionnaire results from studies 301 and 302

		Saline Placebo		Bupivacaine HCl		HTX-011	
Timepoint	Subgroup	N	n (%)	N	n (%)	N	n (%)
Overall	Female	90	27 (30.0%)	139	58 (41.7%)	150	54 (36.0%)
	Male	93	32 (34.4%)	188	83 (44.1%)	169	55 (32.5%)
30 minutes	Female	83	12 (14.5%)	133	19 (14.3%)	143	13 (9.1%)
	Male	87	10 (11.5%)	170	23 (13.5%)	159	18 (11.3%)
1 hour	Female	86	11 (12.8%)	138	13 (9.4%)	148	19 (12.8%)
	Male	93	13 (14.0%)	187	37 (19.8%)	168	27 (16.1%)
2 hours	Female	90	10 (11.1%)	138	8 (5.8%)	148	13 (8.8%)
	Male	92	14 (15.2%)	188	39 (20.7%)	169	28 (16.6%)
4 hours	Female	90	8 (8.9%)	137	11 (8.0%)	149	18 (12.1%)
	Male	93	8 (8.6%)	187	27 (14.4%)	169	25 (14.8%)
18 hours	Female	87	13 (14.9%)	138	19 (13.8%)	148	18 (12.2%)
	Male	93	6 (6.5%)	188	24 (12.8%)	168	14 (8.3%)
24 hours	Female	89	8 (9.0%)	139	21 (15.1%)	150	17 (11.3%)
	Male	92	8 (8.7%)	187	22 (11.8%)	169	13 (7.7%)
72 hours	Female	90	4 (4.4%)	139	14 (10.1%)	149	10 (6.7%)
	Male	92	7 (7.6%)	184	16 (8.7%)	168	9 (5.4%)

Abbreviation: LAST, local anesthetic systemic toxicity.
Note: the table includes any potential symptom based on responses to the LAST assessment questionnaire for Studies 301 and 302.
Source: ISS, Table 18.

Some differences in the potential LAST related AEs between male and female population are identified, however the reported differences are not clinically relevant.

- *Plasma concentration*

Bupivacaine plasma concentrations above 2,000 and 4,000 ng/mL have been associated with neurological and CV effects, respectively (Bardsley 1998; Jorfeldt 1968; Kastrissios 1993; Knudsen

1997; Tucker 1986). For a comprehensive analysis, potential LAST-related TEAEs in subjects administered HTX-011 were evaluated at concentrations of bupivacaine >800, >1,000, >2,000, and >4,000 ng/mL. Maximum plasma concentrations of bupivacaine following administration of HTX-011 in all subjects and in subjects with potential LAST-related TEAEs across Studies 301, 302, 209, and 211 are presented in Table 49.

Table 49: Maximum Concentrations of Bupivacaine Following Administration of HTX-011 and Potential LAST-Related TEAEs in Studies 301, 302, 211, and 209

	Number of Subjects					
	Study 209			Study 211	Study 301	Study 302
	HTX-011 200 mg/6 mg (N = 20)	HTX-011 400 mg/12 mg		HTX-011 400 mg/12 mg (N = 49)	HTX-011 60 mg/1.8 mg (N = 157)	HTX-011 300 mg/9 mg (N = 161)
		No RPV (N = 53)	RPV 50 mg (N = 56)			
All subjects						
BPV C_{max} >800 ng/mL	0	16 (30.2%)	14 (25.0%)	14 (28.6%)	0	5 (3.1%)
BPV C_{max} >1,000 ng/mL	0	10 (18.9%)	7 (12.5%)	5 (10.2%)	0	1 (0.6%)
BPV C_{max} >2,000 ng/mL	0	0	1 (1.8%)	0	0	0
BPV C_{max} >4,000 ng/mL	0	0	0	0	0	0
Subjects with potential LAST-related TEAE	5 (25%)	15 (28.3%)	10 (17.9%)	13 (26.5%)	55 (35.0%)	54 (33.5%)
BPV C_{max} >800 ng/mL	0	6 (11.3%)	5 (8.9%)	2 (4.1%)	0	1 (0.6%)
BPV C_{max} >1,000 ng/mL	0	4 (7.5%)	3 (5.4%)	2 (4.1%)	0	0
BPV C_{max} >2,000 ng/mL	0	0	1 (1.8%)	0	0	0
BPV C_{max} >4,000 ng/mL	0	0	0	0	0	0

Abbreviations: BPV, bupivacaine; C_{max}, maximum observed concentration; LAST, local anesthetic systemic toxicity; RPV, ropivacaine, TEAE; treatment-emergent adverse event.
Note: PK parameters from Study 301 and 302 were estimated using population PK modeling based on the data from of Phase 2 and Phase 3 studies.
Source: Data were derived from Module 5, Section 5.3.5.1, Study 209 CSR, Section 16.1.13.2, HTX-011-209-PK, Table 6-9, Table 6-10, Listing 16.2.7.1; Study 211 CSR, Section 16.1.13.2, HTX-011-211-PK, Table 6-5, Listing 16.2.7.1; Study 301 CSR, Section 16.1.13.1, HTX-011-301-PK, Table 5-1, Listing 16.2.7.1; Study 302 CSR, Section 16.1.13.1, HTX-011-302-PK, Table 5-1, Listing 16.2.7.1.

Three severe dizziness cases were reported from studies 301 and 302; for these subjects, bupivacaine Cmax was reported <500ng/mL. In study 211, one subject experienced tremor and dizziness (plasma concentration of bupivacaine of bupivacaine Cmax >1,000ng/mL) and one experienced dysgueusie (bupivacaine Cmax >1,000ng/mL). In study 209 study (cohort 2) ventricular tachycardia was reported in a subject receiving HTX-011 400 mg/12 mg with ropivacaine 50 mg (bupivacaine Cmax >2,000 ng/mL), 2 subjects reported diziness (Cmax <1,000ng/mL) and 1 reported bradycardia (bupivacaine Cmax <500ng/mL). In cohort 1, one subject experienced 3 moderate to mild dizziness episodes during 3 days (bupivacaine Cmax=500ng/mL). In study 202 one experienced a potential LAST-related TEAE of dizziness resolved within 5 minutes (Cmax bupivacaine >1000ng/mL).

Surgical Wound Healing Assessments

Analysis of surgical wound healing in Phase 3 Studies 301 and 302 and Phase 2b Studies 209 and 211 included the following:

- Assessment of local inflammatory TEAEs,
- Assessment of signs and symptoms associated with abnormal wound healing.

In Phase 2a Studies 202, 203, and 208, surgical wound healing was assessed based on local inflammatory TEAEs.

Surgical wound healing in Studies 302, 209, and 211 was assessed using the Southampton Wound Scoring System. In Study 301, surgical wound healing was assessed based on the presence or absence of the signs and symptoms prespecified by the FDA.

In studies 302, 209 and 211 bruising and erythema were mostly reported. In Study 209 (cohort 1) other sign of inflammation along or around the wound and clear or haemoserous discharge were more reported than other groups, all resolved with a similar frequency than placebo group at day 28.

In study 202, all local inflammatory TEAEs, except erythema, were more reported in HTX-011 groups compared to bupivacaine HCl and placebo groups.

In study 203, in complete-abdominoplasty, local inflammatory TEAEs are similarly reported in HTX-011 400mg/12mg via instillation and placebo group and less reported than bupivacaine HCl 100mg group.

In study 301, HTX-011 groups are more associated with delayed healing, wound dehiscence, incision site oedema, incision site infection and cellulitis compared to bupivacaine HCl 50mg and placebo groups. Delayed healing remains twice more reported after 42 days in HTX-group. Surgical wound healing was not been graded according to Southampton Wound Scoring System, therefore more accuracy assessment of the wound healing in study 301 is not allowed. The applicant justified the over-representation of local inflammatory AEs in HTX-011 60 mg/1.8 mg HTX-011 group compared to the highest dose of HTX-011 doses by the space limits of wound in bunionectomy. The applicant stated that "*the lack of a dose response confirms that HTX-011 has a safety profile comparable to saline placebo and bupivacaine HCl*", which is doubtful. In addition, the applicant provided new outcomes regarding bunionectomy through the study 218 (A Phase 2 Open-Label Study of HTX-011 via Individualized Dosing Administration for Postoperative Analgesia Following Unilateral Simple Bunionectomy) specifically designed to assessed the efficacy and safety with an individualized dose for each subject, precisely because in bunionectomy studies (208 and 301) surgeons noted that amount of HTX-011 drug product was expressed from the surgical site at closure in some subjects and might have resulted in less successful wound closure and/or local inflammatory reactions at the incision site. The mean volume of HTX-011 administered in the 3 studied cohort was 1.62 mL, 1.29 mL, and 1.97 mL (which respectively correspond to 77%, 61% and 94% of the maximum volume recommended in the proposed section 4.2 of Zynrelef SmPC). At any timepoint the number of patients presented "any abnormal result" corresponds to the expected results following a reduction of the volume administrated, namely a decrease of wound healing events depending on the administrated volume. Indeed, the groups "2.1mL" and "1.97mL" shown similar results and the highest wound healing events (respectively 80.9% and 93.9%), and groups "1.62mL" and "1.29" shown the lowest incidence (respectively 70% and 64.7%). On the contrary, in the specific complications such as "delayed healing" and "dehiscence" this trend is not observed and the incidence of these events is more reported in the lowest HTX-011 volume (1.29mL) group following by the "1.97" group and then the 2.1mL group for which the volume appears to be an issue to ensure an optimal wound healing. The administration of HTX-011, regardless of the administrated volume, seems to be a source of complexity for this specific surgery with a restrictive available space. Wound dehiscence and impaired healing were mainly mild in severity, and except one patient with impaired healing, all were resolved without sequalae. The incidence of dehiscence, delayed and impaired healing seems to be correlated with the administration of HTX-011 in bunionectomy.

Regarding the seriousness of wound healing complications (including major complications such as infection) graded according to the Southampton Wound Scoring System for the studies 209, 211 and 302. The results of wound healing assessment shown no major complications (grade IV (i.e. pus) and grade V (i.e. deep or severe wound infection with or without tissue breakdown; haematoma requiring aspiration)) in these studies: only 3 AEs related to wound infection were retrieved in HTX-011 groups with a frequency higher or slightly higher compared to placebo: "incision site cellulitis" (study 209-cohort

1, 1 AE in HTX-011 200/6mg combination group (4.5%) vs 0% in placebo and bupivacaine groups; study 209-cohort 2, 1 AE in HTX-011+ropivacaine group (1.8%) vs 0% in placebo and bupivacaine groups); "post procedural cellulitis" (study 209 cohort 2, 1 AE in HTX-011+ropivacaine group (1.8%) vs 0% in placebo and bupivacaine groups).

No wound healing assessment according to the Southampton Wound Scoring System was provided for the study 301 (symptoms associated with abnormal wound healing were evaluated based on the signs and symptoms prespecified by the FDA in this study), whereas the number of wound infections is more reported in this study in HTX-011 groups versus placebo and bupivacaine HCl groups: "incision site cellulitis" (7 AEs in HTX 60mg/1.8mg (4.5%) vs 1 AE (1%) in placebo group and 2 AEs (1.3%) in bupivacaine group) ; "incision site infection" (4 AEs in HTX 60mg/1.8mg (2.5%) vs 1 AE (0.6%) in bupivacaine group and 0% in placebo group).

In 208 study, the overall local inflammatory TEAEs is more reported in HTX-011 groups than bupivacaine HCl 50mg and placebo groups, especially in HTX-011 120mg/3.6mg group. Individually, except blister, all identified PTs were more reported in HTX-011 groups compared to bupivacaine HCl and placebo groups, and erythema is five times and almost two times more reported in HTX-011 120mg/3.6mg group than, respectively, placebo and bupivacaine HCl 50mg. The applicant stated that "small amounts of HTX-011 drug product were expressed from the surgical site at closure in some subjects potentially impacting the quality of the suturing and causing irritation" and "the surgical site may have been under increased pressure with postoperative swelling and the application of a pressure bandage after surgery. This could result in an increase in local inflammatory TEAEs, including delayed healing and dehiscence". Thus, a large volume administrated into the wound can lead to (1) wound complication and compromise healing and/or (2) conduct to completely cover the wound with pressure bandage leading to a risk of infection. In section 4.2, examples (and no recommendation) of volume to administer are proposed by the applicant for the four surgeries evaluated across Phase 3 and 2b studies; in bunionectomy the dose of 60mg/1.8mg (up to 2.1mL) was given as an example, but surgeons can administer a larger volume. Moreover generally, the sufficient and adequate volume to administer in the surgical site was defined only for 4 surgical procedures, including bunionectomy for which the 120mg/3.6mg was not selected to serve as example of dose to use for this specific surgery. The choice, by surgeons, of the adequate volume to administer to ensure a good wound closure without expressing excess of HTX-011 from the surgical site and with no healing complication in post-surgical period remain difficult to extrapolate for all surgeries as claimed by the applicant (especially those with similar constraints as bunionectomy in terms of amount of space available for the product instillation). Moreover, the selected populations enrolled in 301, 302 and 209 studies present less risk factors (mainly diabetes) of wound complication in HTX-011 groups than placebo group, this risk could be under-estimated.

Study Drug-Related Adverse Events

Investigators assessed AEs as possibly related or unlikely related to study drug. Related TEAEs were defined as TEAEs considered possibly related to study drug. The incidence of related TEAEs was higher in the HTX-011 group compared with saline placebo and bupivacaine HCl (25.2% vs 18.3% and 17.9%, respectively). With the exception of skin odour abnormal and dysgeusia, the incidences of related TEAE PTs were similar across treatment groups. A higher incidence of skin odour abnormal (verbatim term of "body odor") related to study drug was noted in the HTX-011 group compared with the saline placebo and Phase 3 Herniorrhaphy Study for Postoperative Analgesia (EPOCH 2) bupivacaine HCl groups (7.4% vs 1.2% and 0.6%, respectively; all reported at 1 site). The incidence of dysgeusia was also higher in the HTX-011 group compared with saline placebo (7.4% vs 2.4%) but was similar to bupivacaine HCl (8.1%).

Serious adverse event/deaths/other significant events

Phase 3 and Phase 2b Studies

In Phase 3 and 2b, the incidence of SAEs was low and similar for total HTX-011, pooled saline placebo, and total bupivacaine HCl, and ranged from 1.8% to 2.2%. The incidence was slightly higher for HTX-011 400 mg/12 mg (3.7%) and bupivacaine HCl 125 mg (4.6%) (compared with pooled saline placebo (2.0%) and other dose levels of HTX-011 or bupivacaine HCl (ranging from 0% to 1.9%)). There were a total of 30 SAEs: 14 SAEs in 11 subjects (2.2%) administered HTX-011, 8 SAEs in 7 subjects (1.8%) administered bupivacaine HCl, and 8 SAEs in 5 subjects (2.0%) administered saline placebo.

Serious TEAEs are similarly reported between HTX-011, bupivacaine and placebo groups across Phase 3 and 2b studies. Fourteen serious TEAEs were reported, including 3 not related to study drug, 2 of them reported alternative explanations (breast implant perforated during the surgery; thoracic vertebral fracture after fall at home) or with a reasonable incompatible chronology (diagnosis of bile duct and intestinal perforation few hours after receiving HTX-011). Two subjects experienced serious post procedural complication (Incision site haematoma, resolved after 1 day and cellulitis, resolved after 10 days).

Phase 2a studies

In phase 2a studies, there were a total of 8 SAEs in 8 subjects: 4 SAEs in 4 subjects administered HTX-011, 2 SAEs in 2 subjects administered bupivacaine HCl, and 2 SAEs in 2 subjects administered saline placebo. No SAEs occurred in subjects who were administered study drug by instillation only.

Death

There was 1 death across the entire clinical program, in a subject who had received bupivacaine HCl in Study 301. The cause is unknown, but the death was considered by the Investigator not related to study drug.

Laboratory findings

Hematology Parameters in Phase 3 and Phase 2b studies

Hematology parameters presented in this section were selected based on the proportions of subjects with shifts in values from normal at Baseline to low post-Baseline or from normal at Baseline to high post-Baseline.

- *Shifts from normal at baseline to low post-baseline in hematology parameters*

In Phase 3 and 2b studies, the incidences of shifts from normal at Baseline to low at any time post-Baseline for RBC count, Hct, Hgb, lymphocyte differential, and lymphocyte count were higher for HTX-011 400 mg/12 mg and 200 mg/6 mg and bupivacaine HCl 125 mg compared with other treatment groups. HTX-011 200 mg/6 mg and 400 mg/12 mg and bupivacaine HCl 125 mg were used in TKA in Study 209 and HTX-011 400 mg/12 mg was used in mammoplasty in Study 211. However, these changes were driven by TKA; the changes in mammoplasty were similar to those for pooled analysis.

In Study 209, there were no clinically meaningful differences between treatment groups in shifts from normal at Baseline to low post-Baseline in hematology parameters. Incidence of shifts from normal at Baseline to low at post-Baseline for RBC count, Hct, and Hgb for HTX-011 400 mg/12 mg and 200 mg/6 mg and bupivacaine HCl 125 mg increased at 72 hours compared with 24 hours and then decreased at Day 10. A similar trend was observed for pooled saline placebo. TKA is associated with a greater blood loss compared with mammoplasty, bunionectomy and herniorrhaphy. Thus, the observed shifts for RBC count, Hct, and Hgb are consistent with those expected after TKA. However, no clinically meaningful differences in incidences of TEAEs of anaemia postoperative, anaemia, red blood cell count decreased, haematocrit decreased, and haemoglobin decreased between treatment groups were observed. The incidences of shifts from normal at Baseline to low at post-Baseline for lymphocyte differential and lymphocyte count for HTX-011 400 mg/12 mg and 200 mg/6 mg and bupivacaine HCl 125 mg were the highest at 24 hours and decreased at 72 hours and Day 10.

- *Shifts from normal at baseline to high post-baseline in hematology parameters*

The incidences of shifts from normal at Baseline to high at any time post-Baseline for WBCs, neutrophil count, neutrophil differential, and platelet count (on Day 10 only) were higher for HTX-011 400 mg/12 mg and 200 mg/6 mg and bupivacaine HCl 125 mg compared with other treatment groups. HTX-011 200 mg/6 mg and 400 mg/12 mg and bupivacaine HCl 125 mg were used in TKA in Study 209 and HTX-011 400 mg/12 mg was used in mammoplasty in Study 211. In Studies 209 and 211, there were no clinically meaningful differences between treatment groups in shifts from normal at Baseline to high post-Baseline in hematology parameters.

Incidences of shifts from normal at Baseline to high post-Baseline for WBCs, neutrophil differential, and neutrophil count for HTX-011 400 mg/12 mg and 200 mg/6 mg and bupivacaine HCl 125 mg were generally the highest at 24 hours and then decreased at 72 hours and Day 10. The applicant has provided discussion on reported shifts from baseline to high at 24h, 72 h and 10 days timepoints WBC count, neutrophil differential and neutrophil counts in HTX-011 group compared to placebo. The applicant argued that, from the one hand these findings are likely related to surgery type, and from the other hand no clinically meaningful related adverse effects were observed (such as infections or infestations). In light of this, it was concluded that these findings do not change the risk/benefit profile for IMP.

A similar trend was observed for pooled saline placebo. For WBCs, this finding is consistent with a higher incidence of leukocytosis for HTX 400 mg/12 mg compared with pooled saline placebo (6.7% compared with 0.8%). A TEAE of neutrophilia was reported for 1 subject administered HTX-011 400 mg/12 mg. The overall incidence of infections and infestations was similar in all treatment groups. No TEAEs of incision site infection or postoperative wound infection were reported in subjects administered HTX-011 400 mg/12 mg or 200 mg/6 mg or bupivacaine HCl 125 mg. Shifts from normal at Baseline to high post-Baseline for HTX-011 400 mg/12 mg and 200 mg/6 mg and bupivacaine HCl 125 mg for platelet counts were observed at Day 10 only. A similar trend was observed for pooled saline placebo. There were no

TEAEs of deep vein thrombosis, deep vein thrombosis postoperative, venous thrombosis, or thrombophlebitis for HTX-011 400 mg/12 mg or 200 mg/6 mg or bupivacaine HCl 125 mg. Incidences of a TEAE of thrombocytosis were similar for all treatment groups.

In Study 209 in TKA in Cohort 2, two subjects administered HTX-011 400 mg/12 mg and 1 subject administered bupivacaine HCl 125 mg experienced TEAEs of pulmonary embolism; they were reported as SAEs. None of these 3 subjects had an elevated platelet count on or near the day of the onset of SAEs; 1 subject administered HTX-011 400 mg/12 mg had a low platelet count (141 × 109/L) at the onset of the pulmonary embolism on Day 3. All 3 SAEs were considered by the Investigator unlikely related to study drug and all resolved.

Hematology Parameters in Phase 1 and Phase 2a Studies

In Phase 2a Studies (202, 203 and 208), no clinically meaningful changes in mean absolute values or mean changes from Baseline for any hematology parameter were observed. There were no clinically meaningful differences between treatment groups in the proportion of subjects with a shift from Baseline in hematology parameters.

In Study 102, no clinically meaningful changes in hematology parameters or shifts from Baseline were observed.

Clinical Chemistry Parameters

There were no clinically meaningful differences between treatment groups with respect to either mean changes from Baseline in hematology and clinical chemistry parameters, individual subject shifts from Baseline, or associated TEAEs. Observed differences across treatment groups appeared to reflect the different surgical settings (and study populations) in which specific doses were used, rather than being directly related to the dose of HTX-011 or bupivacaine HCl.

The incidence of prespecified liver function test abnormalities was similar across the HTX-011, bupivacaine HCl, and saline placebo treatment groups, and no subject met the criteria for Hy's Law.

Vital Signs, Physical Findings, and Other Observations Related to Safety

In the pooled Phase 3 and Phase 2b safety dataset, there were no clinically meaningful differences between treatment groups with respect to either mean changes from baseline in vital signs, the incidences of prespecified clinically relevant vital sign abnormalities, or the incidences of associated TEAEs.

To evaluate the effect of HTX-011 on the QTcF interval, multiple regression analyses were performed to evaluate the relationship between derived QTcF interval and plasma concentrations of bupivacaine HCl and meloxicam in Studies 209, 211, 301, and 302.

There were no consistent or clinically meaningful differences in ECGs between treatment groups. HTX-011 did not affect QTcF interval, HR, PR interval, and QRS interval based on concentration-effect modeling (Section 3.4.2), central tendency analysis, or outlier categorical frequencies. In Study 209, administration of another local anesthetic, ropivacaine 50 mg, with HTX-011 400 mg/12 mg had no effect on ECG intervals, did not prolong the QTcF interval, nor produce any other adverse ECG effects when compared with HTX-011 400 mg/12 mg administered without ropivacaine.

The applicant report no meaningful ECG findings (heart rate, PR, RR, QRS and change from baseline in QT intervals) between treatment groups in pivotal and supportive studies.

Bone Healing Assessments

Bone healing was assessed in Study 301 and Study 208 in bunionectomy.

In study 301, X-rays of the surgical site were performed at the Day 28 and Day 42 Visits to assess bone healing. Bone healing symptoms were recorded as normal, mal-union, or delayed healing. The majority of subjects had normal bone healing on Day 28 (99.0%) and on Day 42 (98.5%).

Mal-union was reported for 3 subjects administered HTX-011 60 mg/1.8 mg; none was reported for subjects administered saline placebo or bupivacaine HCl 50 mg. Of the 3 mal-unions in subjects administered HTX-011, 2 were reported as TEAEs. Both TEAEs resolved and were considered by the Investigator unlikely related to study drug.

Delayed bone healing was reported for 4 subjects: 1 administered saline placebo, 2 administered bupivacaine HCl 50 mg, and 1 administered HTX-011 60 mg/1.8 mg. Three of the 4 TEAEs, including the TEAE in 1 subject administered HTX-011 60 mg/1.8 mg, were considered by the Investigator unlikely related to study drug and resolved.

In Study 208, bone healing was assessed within 4 to 6 weeks following the surgery by X-ray and was evaluated as normal or improper. One subject administered HTX-011 120 mg/3.6 mg had improper bone healing on Day 29. It was reported as mal-union due to non-compliance with postoperative therapy ("premature unprotected weight bearing with rapid return to work"). The abnormal bone healing was considered by the Investigator not related to study drug).

No specific safety issue emerged from the reported cases of bone healing impairment in phase 2b and 3 studies in bunionectomy. One improper bone healing (in study 208) and 3 bone mal-union (in study 301) were in HTX-011 groups; all reported noncompliance with postoperative therapy (i.e. premature weight bearing, rapid return to work or activities with no adequate protections) or following an accident.

Safety in special populations

Effect of age

In general, the incidences for any TEAE, any TEAE possibly related to study drug, any SAE, any ORAE, any local inflammatory TEAE, or any potential LAST-related TEAE for the <65 years subgroup were similar to the total population including both age groups for the pooled saline placebo, total bupivacaine HCl, and total HTX-011 groups.

The incidences of any TEAE, any SAE, and any ORAE by age subgroup (≥65 years and <65 years) were similar for the total HTX-011 and pooled saline placebo groups.

Although similar, the incidences of SAEs were slightly higher for the ≥65 years age group compared to the <65 years age group for the total HTX-011 (5.2% vs 1.5%) and pooled saline placebo groups (5.6% vs 1.4%).

The number of subjects with local inflammatory TEAEs for the ≥65 years age group was low with the highest incidence for the HTX-011 60 mg/1.8 mg group (8 of 24, 33.3%) from the bunionectomy study.

For the ≥65 years subgroup, the incidence of any potential LAST-related TEAE was highest for the pooled saline placebo group (41.7%) as compared to the total bupivacaine HCl group (36.0%) and total HTX-011 group (26.0%) and higher than any HTX-011 dose group (20.0% to 37.5%). The number of subjects with any potential LAST-related TEAE for the ≥65 years age group was low, with the highest incidence for the bupivacaine HCl 75 mg group (6 of 11, 54.5%) from the herniorrhaphy study.

Effect of Sex

In general, the incidences for any TEAE for the female subgroup and the male subgroup were similar across the pooled saline placebo, total bupivacaine HCl, and total HTX-011 groups as compared to the total population that included both sexes.

The proportions of subjects in the total HTX-011, pooled saline placebo, and total bupivacaine HCl groups with any TEAE, any ORAE or any local inflammatory TEAE was slightly higher for females compared with males. The incidences of potential LAST-related TEAEs were not consistent and were higher for females for the total HTX-011 group, higher for males for the total bupivacaine HCl group, and similar between females and males for the pooled saline placebo group. The incidence of SAEs was low and similar for females and males across treatment groups.

Effect of Race

In general, the incidences for any TEAE, any ORAE, any local inflammatory TEAE, and any potential LAST-related TEAE for the White subgroup were similar across the pooled saline placebo, total bupivacaine HCl, and total HTX-011 groups and for each treatment group by dose as compared to the total population including all races.

Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies were conducted with HTX-011. The section 4.5 of the Zynrelef SmPC is based on the approved SmPC of each component of the combination.

Discontinuation due to adverse events

HTX-011 is intended for a single-dose application, therefore the large majority or subject (>95%) completed the studies, and only 3 subjects "withdrew" from one study (one in the low-dose arm and two in the higher-dose arms) due to safety reasons. In view of the pattern of HTX-011 administration (installation in the surgical site prior to closure, which define the Day 0 of the study), no true withdrawal is expected in HTX-011 studies.

In the Phase 3 and Phase 2b studies, 3 subjects experienced a TEAE that led to withdrawal from the study following the administration of HTX-011 (vs. one in placebo groups, withdrew due to an uncontrolled pain after undergoing a unilateral TKA (study 209)). The TEAEs in subjects administered HTX-011 that led to withdrawal from the study were as follows:

- In Study 301, one subject administered HTX-011 60 mg/1.8 mg developed a bile duct stone after surgery. The event was serious, and the subject was withdrawn from the study on Day 2. The subject underwent surgery to have the stone removed on Day 4, and the event was considered resolved. The event was considered by the Investigator unlikely related to study drug and cited the subject's prior history of gallstones and a gastric ulcer as contributing factors.
- In Study 209, one subject administered HTX-011 400 mg/12 mg with ropivacaine 50 mg experienced an SAE of severe urinary retention on Day 1 that resulted in withdrawal from the study. The urinary retention resolved approximately 3 months after the onset and was considered by the Investigator unlikely related to study drug.
- In Study 209, one subject administered HTX-011 400 mg/12 mg with ropivacaine 50 mg experienced an SAE of moderate pulmonary embolism on Day 3 that resulted in withdrawal from the study. The event resolved on Day 9 and was considered by the Investigator unlikely related to study drug.

There were no TEAEs that led to "withdrawal" in Phase 2a studies.

Post marketing experience

HTX-011 is not marketed in any country. Bupivacaine and meloxicam, the active ingredients in HTX-011, are approved in Europe, the US, and other regions, and have a long history of clinical use. An extensive review of clinical literature on toxicities of bupivacaine and meloxicam was conducted by the applicant (searching period: from 1966 to 2018 for bupivacaine and from 1990 to 2018 for meloxicam).

Literature Review for Bupivacaine

The known toxicities of bupivacaine have been well documented in the literature and mainly consist of clinical neurotoxicity involving seizure activity and cardiovascular toxicity consisting of cardiac arrhythmias and cardiac arrest, which is often refractory to standard cardiopulmonary resuscitation but responsive to lipid emulsion therapy. This report found multiple reports of cardiotoxicity, neurotoxicity, chondrolysis, and case reports of dermatologic, allergic, and hepatic toxicities.

In this literature review multiple less typical but previously documented adverse effects have been found. Many of these adverse effects are secondary to inadvertent administration of bupivacaine into unintended anatomic areas or spaces or idiosyncratic reactions in the cases of hepatic dysfunction or allergic type reactions.

Literature Review for Meloxicam

NSAIDs are known for multiple adverse effects, including GI bleeding, cardiovascular side effects, and NSAID-induced nephrotoxicity. Review of the clinical data found clinical reports of meloxicam-related hypertension, drug interactions, and drug intolerance/allergies.

This review confirmed the known adverse effects of meloxicam as an NSAID. The majority of the data is supportive of the relative safety of meloxicam as compared to other NSAIDs for cardiovascular and GI adverse effects. The data for allergic reactions to NSAIDs is highly suggestive for a low risk of cross-reactivity in individuals who have a demonstrated reaction to aspirin or other NSAIDs.

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials literature have been included in the Summary of Product Characteristics.

During Phase 2 and 3 studies, 1067 subjects received a single dose of HTX-011-XX (all formulations and administration techniques). Among them, 504 received HTX-011 via installation in Phase 3 and 2b studies, more than 100 subjects in Phase 2a (considered as supportive) and 20 in Phase 1. The overall number of subjects enrolled in HTX-011 studies is considered sufficient for HTX-011 safety evaluation. Demographic characteristics of the safety population included age, gender, race, ethnicity and BMI. In general, the demographic and baseline characteristics are similar between respective HTX-011, bupivacaine HCl and placebo groups in each study. No subject under 18 years-old and 136 subjects older than 65 years were enrolled in HTX-011 development program.

The population targeted by Zynrelef in the indication claimed by the applicant is broad. In consequence, demographic and baseline characteristics are variable according to the type of surgery (mammoplasty, bunionectomy, TKA and herniorrhaphy). Populations enrolled in each study seem to be representative of each type of surgery. Non-homogeneity in subjects' history have been noted (in 302 study and cohort 1 of 209 study, subjects receiving HTX-011 reported respectively less history of cardiac and cardiovascular disorders than placebo and/or bupivacaine HCl groups; diabetes is less reported in HTX-011 groups than

bupivacaine HCl and placebo groups in studies 301, 302 and in study 209 cohort 1) and may an impact on under-estimation of cardiovascular events and wound healing.

In general, the incidence and severity of TEAEs and the incidence of SAEs reported across placebo, bupivacaine HCl and HTX-011 groups is quite similar, except for local TEAEs and LAST-related TEAEs.

TEAEs onset seems to be specific to each dose and surgery. In Phase 3 and 2b studies, the most TEAEs reported in HTX-011 groups (more than 5% of all subjects receiving HTX-011) and with an slightly higher incidence than placebo are: constipation (17.3% in HTX-011 vs. 14.6% in placebo group), vomiting (16.9% vs. 15%), headache (11.7% vs. 8.9%), tachycardia (6.5% vs. 5.3%), bradycardia (6.0% vs.4.9%). All subjects in Phase 2b studies (209 and 211), 71.3% of subjects in 301 study and 48.5% in 302 study received rescue medication, upon request, for pain control (mainly oxycodone, morphine, fentanyl) during the 72-hours postoperative period. The role of the systematic use of opioids during the 72-hours postoperative period in these major surgeries (mammoplasty, TKA) cannot be ruled out in "constipation", "vomiting" and "headache" onset. Among opioid-free subjects in study 302, the frequency of local inflammatory AEs is higher in the HTX-011 group than placebo group (6% vs. 0%), as well as the following AEs: "skin odour abnormal" (11.9% vs. 0%), "dysgeusia" (11.9% vs. 0%) and "bradycardia" (9.5% vs. 5.6%). All these AEs are reflected in the proposed section 4.8 of Zynrelef SmPC. The applicant considered the following TEAEs as drug-related, and added these TEAEs to the proposed section 4.8: "dysgeusia", "skin odour abnormal", "dizziness", "injection site reaction", "hypotension" and "bradycardia". Regarding the potential gastrointestinal effect of meloxicam, no specific issue was identified, except 2 cases of haematochezia (in studies 209 and 301) considered unlikely drug-related by the investigator.

Regarding LAST-related TEAEs, in studies 301 and 302, dizziness, bradycardia, hypotension, dysgeusia, muscle twitching, were reported as more frequent compared to the placebo group, but with a similar frequency than the bupivacaine HCl control groups. Taken individually, some of LAST-TEAEs are identified more frequently in HTX-011 groups than placebo and with a similar or higher frequency than bupivacaine groups (namely "hypotension", "bradycardia" and "tinnitus" in study 209 cohort 2; "hypotension" in study 211; "dizziness", "bradycardia", "hypotension" in study 301; "bradycardia", "dysgeusia", "paresthesia"/"paresthesia oral", "sinus arrhythmia", "vision blurred", in study 302). As mentioned by Vasques, MD et al.[4] (2015), "confusion, dizziness, tinnitus, dysgeusia, hallucinations, slurred speech, gait problems, limb twitching, extremity paresthesia, intention tremor, hypotonia, and facial sensorimotor and eye movement abnormalities [are minor central nervous system (CNS) abnormalities] and defined as prodromal manifestations of toxicity when they occurred either alone or before major signs of toxicity". The authors identified these prodromal signs as the most frequent CNS manifestations of LAST. Similarly, they identified hypotension and bradycardia as the most frequent signs of cardiovascular toxicity.

In 203 study, 5 subjects reported TEAEs potentially suggestive of LAST in the HTX-011 400mg/12mg group by instillation: 2 subjects experienced "dizziness", one subject "bradycardia", one subject "paresthesia" and one subject "tinnitus" (which belong to possible symptom of bupivacaine-related CNS toxicity). In study 211, one subject experienced tremor and dizziness (plasma concentration of bupivacaine of bupivacaine Cmax >1,000 ng/mL) and one experienced dysgeusia (bupivacaine Cmax >1,000 ng/mL). In study 209 study (cohort 2) ventricular tachycardia was reported in a subject receiving HTX-011 400 mg/12 mg with ropivacaine 50 mg (bupivacaine Cmax >2,000 ng/mL), 2 subject reported dizziness (Cmax <1,000 ng/mL) and 1 reported bradycardia (bupivacaine Cmax <500 ng/mL). In study 202 one subject experienced a potential LAST-related TEAE of dizziness resolved within 5 minutes (Cmax bupivacaine >1000 ng.mL). As expected, higher plasma concentrations of bupivacaine were associate

[4] Vasques F, Behr AU, Weinberg G, Ori C,Di Gregorio G. A Review of Local Anesthetic Systemic Toxicity Cases Since Publication of the American Society of Regional Anesthesia Recommendations: To Whom It May Concern. Regional Anesthesia and Pain Medicine 2015; 40(6): 698-705.

with the highest incidence of LAST-related TEAEs (30% in subjects for which bupivacaine Cmax > 800 ng/mL; 41% with Cmax > 1000 ng/mL; 100% with Cmax > 2000 ng/mL). Ventricular tachycardia, tremor, severe dizziness pertained to the list of signs or symptoms suggestive of cardiovascular or central nervous system toxicity of bupivacaine. These potential risks are adequately labelled in section 4.4 of the proposed Zynrelef SmPC. The incidences of potential LAST-related TEAEs with rapid onset (less than 1 hour) in HTX-011 groups in Phase 2b and 3 studies were similar to those for bupivacaine HCl. Taking into account that the Tmax of bupivacaine HCl is approximately 1 hour and the Tmax of bupivacaine contained in Zynrelef is 4 hours minimum and the theoretical release of bupivacaine during 72 hours, the similar incidence of the majority of rapid LAST-related AEs, especially in study 302 (HTX-011 300 m/9mg vs. bupivacaine HCl 75 mg group), remains not fully explained and clarified. The causal relationship between Cmax and occurrence of LAST-related events is difficult to demonstrate based on the data provided by the applicant. In a general way regarding ALST-related-TEAEs, the applicant use the threshold plasma concentration of bupivacaine of 2,000 ng/mL as unique criteria to characterize an AE as LAST or not, this approach is questionable.

Regarding surgical wound healing in bunionectomy studies, in study 301, HTX-011 groups are more associated with delayed healing, wound dehiscence, incision site oedema, incision site infection and cellulitis compared to bupivacaine HCl 50mg and placebo groups. Delayed healing remains twice more reported after 42 days in HTX-group. Surgical wound healing was not been graded according to Southampton Wound Scoring System, whereas the number of wound infections is more reported in this study in HTX-011 groups versus placebo and bupivacaine HCl groups: "incision site cellulitis" (7 AEs in HTX 60 mg/1.8mg (4.5%) vs 1 AE (1%) in placebo group and 2 AEs (1.3%) in bupivacaine group) ; "incision site infection" (4 AEs in HTX 60 mg/1.8mg (2.5%) vs 1 AE (0.6%) in bupivacaine group and 0% in placebo group). The applicant provided new outcomes regarding bunionectomy through the study 218 (A Phase 2 Open-Label Study of HTX-011 via Individualized Dosing Administration for Postoperative Analgesia Following Unilateral Simple Bunionectomy) specifically designed to assessed the efficacy and safety with an individualized dose for each subject, precisely because in bunionectomy studies (208 and 301) surgeons noted that amount of HTX-011 drug product was expressed from the surgical site at closure in some subjects and might have resulted in less successful wound closure and/or local inflammatory reactions at the incision site. The mean volume of HTX-011 administered in the 3 studied cohort was 1.62 mL, 1.29 mL, and 1.97 mL (which respectively correspond to 77%, 61% and 94% of the maximum volume recommended in the proposed section 4.2 of Zynrelef SmPC). For the specific complications such as "delayed healing" and "dehiscence" the incidence of these events is more reported in the lowest HTX-011 volume (1.29 mL) group following by the "1.97 mL" group and then the 2.1 mL group for which the volume appears to be an issue to ensure an optimal wound healing. The administration of HTX-011, regardless of the administrated volume, seems to be a source of complexity for this specific surgery with a restrictive available space.

In 208 study, the overall local inflammatory TEAEs is more reported in HTX-011 groups than bupivacaine HCl 50 mg and placebo groups, especially in HTX-011 12 0mg/3.6 mg group. Individually, except blister, all identified PTs were more reported in HTX-011 groups compared to bupivacaine HCl and placebo groups, and erythema is five times and two times more reported in HTX-011 120 mg/3.6 mg group than, respectively, placebo and bupivacaine HCl 50 mg. The applicant states that "*small amounts of HTX-011 drug product were expressed from the surgical site at closure in some subjects potentially impacting the quality of the suturing and causing irritation*" and "*the surgical site may have been under increased pressure with postoperative swelling and the application of a pressure bandage after surgery. This could result in an increase in local inflammatory TEAEs, including delayed healing and dehiscence*". Thus, a large volume administrated into the wound can lead to wound complication and compromise healing and/or conduct to completely cover the wound with pressure bandage leading to a risk of infection. In section 4.2, examples (and no recommendation) of volume to administer are proposed by the applicant for the four surgeries evaluated across Phase 3 and 2b studies; in bunionectomy the dose of 60

mg/1.8mg (up to 2.1 mL) was given as an example, but surgeons can administer a larger volume. Moreover generally, the sufficient and adequate volume to administer in the surgical site was defined in Phase 3 and 2 studies only for 4 surgical procedures, including bunionectomy for which the 120 mg/3.6 mg was not selected to serve as example of dose to use for this specific surgery. The choice, by surgeons, of the adequate volume to administer to ensure a good wound closure without expressing excess of HTX-011 from the surgical site remain difficult to extrapolate for all surgeries as claimed by the applicant, especially those with similar constraints in the available amount of space for the product instillation as bunionectomy. Moreover, the selected populations enrolled in 301, 302 and 209 studies present less risk factors (mainly diabetes) of wound complication in HTX-011 groups than placebo group, this risk could be under-estimated.

In studies 302, 209 and 211 bruising an erythema were mostly reported. In study 209 (cohort 1) other sign of inflammation along or around the wound and clear or haemoserous discharge were more reported than other groups, all resolved with a similar frequency than placebo group at day 28. In study 202, all local inflammatory TEAEs, except erythema, were more reported in HTX-011 groups compared to bupivacaine HCl and placebo groups.

Wound dehiscence and impaired healing are mainly mild in severity, and except one patient with impaired healing, all were resolved without sequalae.

No specific safety issue emerged regarding bone healing impairment. Four subjects experienced bone healing or bone mal-union in study 301 and 208 in bunionectomy, but all reported non-compliance with postoperative therapy or following an accident.

Serious TEAEs are similarly reported between HTX-011, bupivacaine and placebo groups across Phase 3 and 2b studies. Fourteen serious TEAEs were reported, including 3 not related to study drug, 2 of them reported alternative explanations (breast implant perforated during the surgery; thoracic vertebral fracture after fall at home) or with a reasonable incompatible chronology (diagnosis of bile duct and intestinal perforation few hours after receiving HTX-011). Two subjects experienced serious post procedural complication (Incision site haematoma, resolved after 1 day and cellulitis, resolved after 10 days). No fatal case was reported in all HTX-011 groups.

Anaemia was reported with the higher incidence in the 400 mg/ 12 mg HTX-011 (5.2% v 1.9% in saline group and 0 in bupivacaine HCL group) in phase 3 study. The applicant stated that this AE is more likely associated with the type of the surgery. However, given that meloxicam belongs to NSAID class, possible effects on coagulation processes must considered. Gastrointestinal bleeding was indicated as an AE of special interest by the applicant due to pharmacological effects of meloxicam. Four events of GI bleeding were reported in the HTX-011 group, though all were considered not HTX-011 treatment related by the investigator.

Overall significant shifts from baseline to high at 24h, 72 h and 10 days timepoints were reported for WBC count, neutrophil differential and neutrophil counts in HTX-011 group compared to placebo. WBCs, neutrophil differential, and neutrophil counts were the highest at 24 hours and then decreased at 72 hours and Day 10 in both placebo and HTX-011 group. However, difference in shifts from baseline to high for WBC count, neutrophil differential and neutrophil counts reported in HTX-011 group compared to placebo was not properly discussed by the applicant. As requested, the applicant has provided discussion on these findings and argues that, from the one hand these findings are likely related to surgery type, and from the other hand no clinically meaningful related adverse effects were observed (such as infections or infestations). In light of this, it was concluded that these findings do not change the risk/benefit profile for Zynrelef.

Evaluation of hepatic function has been performed in line with FDA's Guidance for Industry. Clinical chemistry parameters were evaluated based on proportions of subjects with shifts in values from normal

at baseline. No clinically meaningful differences were observed comparing pooled HTX-011 group and placebo group, as well as data reported from supportive Phase 1 and 2a studies. Observed deviations from baseline levels in hepatic and renal parameters were not associated with TEAEs.

Higher rates in shift from normal baseline to high was reported for ALP in HTX-011 400 mg/12 mg and 200 mg/6 mg and bupivacaine HCl 125 mg at Day 10 compared with 72 hours. A similar trend was observed also for pooled saline placebo. Increased levels in ALP were observed following TKA. Since ALP is commonly used osteoblast marker these findings were explained by specific type of surgery (TKA), what is generally agreed. The only evaluated parameter characterizing renal function was blood urea nitrogen (BUN). No clinically meaningful differences in shifts from baseline were observed between HTX-011 and placebo groups.

The provided data do not suggest significant difference in the safety profile depending on patients age. In HTX-011 group any TEAEs were reported with slightly higher incidence in patients > 65 years. Overall incidence of any TEAEs was similar between patients below and above 65 years in total bupivacaine group. Incidence of local inflammatory TEAEs was slightly higher in patients > 65 years in HTX-011 group, but significantly lower in total bupivacaine HCL group and similar in placebo group. Lower incidence of any potential LAST related AEs was reported in patients > 65 years.

No studies on potential drug-drug interactions were conducted with HTX-011. Safety information relating to drug-drug interactions was based on information provided in the SmPC for already approved products: Marcaine and bupivacaine solution for injection 2.5 mg/mL and 5 mg/mL and and Melox 10 mg/mL solution for injection (Meloxicam Injection SmPC 2017). The potential drug-drug interactions were not evaluated and discussed within the scope of pooled safety assessment provided in support of this MA submission. Although, both active substances are well known with established safety profile, information on potential effects of concomitant use of HTX-011 and other drugs of interest would be valuable for further risk/benefit assessment. As requested, the applicant provided the detail of subjects who were administered a drug that could interfere with hemostasis and a brief analysis of TEAEs occurred in these subjects. Based on the presented data, any specific safety risks were not identified in subject with perioperative exposure to drugs that interfere with hemostasis or loop diuretics.

The following uncertainties remain: the safety profile seems to be variable depending on the type of surgery and the characteristics of surgical site (systemic exposure to bupivacaine may vary depending on the vascularised area, size of the wound and amount of space available for Zynrelef leading to complications).

2.6.2. Conclusions on the clinical safety

In general, Zynrelef displays a risk profile corresponding to well-known substances used in the fixed combination. In the development program of HTX-011, the safety of the product was evaluated in only 4 surgical procedures involving specific doses (ranging from 60 mg/1.8 mg to 400 mg/12 mg) corresponding to specific volume to instil directly in the wound before suturing (ranging from 2.1 to 14 mL) in populations mainly receiving rescue medication (opioids). No specific safety issue which can be related to meloxicam was identified, but although it seems that the risk of AEs related to systemic exposure to meloxicam is rather low, possibility of such risk should not be underestimated, especially in specific subpopulations. Two specific concerns remain as uncertainties.

The first concern is related to the passage of bupivacaine into the bloodstream and compatible with the potential onset of LAST-related TEAEs (CNS and CV). Despite of the fact that Zynrelef allows to avoid the use of inadvertent intravascular injection and limit bupivacaine systemic exposure, high plasma concentrations of bupivacaine associated with LAST-related TEAEs have been identified and the incidence of certain LAST-related and rapid onset (less than 1 hour) LAST TEAEs is quite similar between HTX-011

and bupivacaine HCl groups. Zynrelef being use in a single administration, the dose cannot be reduced after instillation to better manage AEs.

The second concern is related to the administration of an "adequate volume" of the product in the surgical site to ensure both a good wound closure with no dehiscence and no expression of an excess of Zynrelef from the surgical site. In a surgery with a restrictive available amount of space for ensuring a complete instillation such as bunionectomy, even a reduction of the volume instilled seems not to ensure conclusive results on wound healing complications. In order to further monitor and characterize this risk, "wound healing complications" should be included as an "important potential risk" in the Zynrelef RMP, at least to closely monitor this concern in post-marketing experience in PSURs.

The safety profile seems to be variable depending on the type of surgery and the characteristics of surgical site (vascularisation, size of the wound and amount of space available for HTX-011).

Risk Management Plan

Safety concerns

Summary of safety concerns

Table 50

Important identified risks	None
Important potential risks	Wound healing impairment
Missing information	Use in breast feeding women

Pharmacovigilance plan

Routine pharmacovigilance is considered sufficient to monitor the safety of the product in the approved indication.

No additional PV activities are envisaged for bupivacaine / meloxicam.

Risk minimisation measures

Table 51: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
None	N/A	N/A
Important potential risks		
Wound healing impairment	Routine risk minimisation measures: *SmPC section 4.2* *SmPC section 4.8* *PL section 2* *PL IFU* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Missing information		
Use in breast feeding women	Routine risk minimisation measures: *SmPC section 4.6 PL section 2* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.0 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Based on fact that Zynrelef is a new combination in a new formulation, the CHMP is of the opinion that a separate entry in the EURD list for Zynrelef is needed, as it cannot follow the already existing entry for bupivacaine only. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request the alignment of the new PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

Based on a justification mainly relating to the limited space of the immediate container, the Group agreed to allow minimum particulars on the 20 mL vial label. The Group also agreed not to repeat the route of administration provided the final EDQM agreed terms for the pharmaceutical form reflect the route of administration. The latter condition was not fulfilled as the finally agreed terms for the pharmaceutical form '*prolonged-release wound solution*' did not reflect the route of administration (intralesional use). The RoA shall be reflected in the vial label.

3. Benefit-Risk Balance

3.1.1. Disease or condition

Zynrelef is intended for treatment of postoperative pain. Up to 70% of patients have moderate to severe pain after surgery and the most severe pain occurs within the first 72 hours.

3.1.2. Available therapies and unmet medical need

Postoperative pain management practice guidelines and clinical studies endorse the use of a multimodal or balanced approach defined as the use of multiple antinociceptive agents with different mechanisms of action. That is, pain is best managed using a combination of methods including regional anesthetic and analgesic techniques (e.g. nerve blocks, local wound infiltrations, epidural catheters) along with systemically administered drugs (Schurr 2004). Generally, a systemic opioid is complemented by one or more adjuvant agents (Meissner 2015).

Opioids use is a major element of postoperative pain management. However, as the single therapeutic entity causes significant problems such as ventilatory impairment, sedation, nausea and vomiting, and delayed recovery of bowel function. These adverse effects endanger patient safety and/or impair recovery and rehabilitation and thereby delay discharge from hospital.

The recognised advantages of multimodal analgesia are the following: improved analgesia, reduced opioids requirements and reduced adverse effects of opioids.

Bupivacaine HCl is a common medicine used for post-surgical analgesia as one of the long acting local anaesthetics, but even so it has a limited duration of action after local administration, usually reported as less than 8-12 hours.

Alternative local anaesthetic treatment options are needed as part of multimodal therapy to better manage post-surgical pain that offer extended duration and greater magnitude of analgesic effects.

3.1.3. Main clinical studies

The main evidence for efficacy submitted is two phase 3 multicentre, randomized double-blind, placebo- and active-controlled comparing:

- HTX-011 60 mg / 1.8 mg (2.1 mL) administered via instillation (n=157) vs saline placebo (2.1 mL) administered via instillation (n=100) or bupivacaine 0.5%, 50 mg (10 mL) administered via injection (n=155) in adult subjects undergoing primary unilateral, distal, first metatarsal bunionectomy with osteotomy and internal fixation.
- HTX-011 300 mg / 9 mg (10.3 mL) administered via instillation (n=164) vs saline placebo (10.3 mL) administered via instillation (n=82) or bupivacaine 0.25%, 75 mg (30 mL) administered via injection (n=172) in adult subjects undergoing unilateral open inguinal herniorrhaphy.

In addition, one cohort of a phase 2 study has been classified as pivotal by the applicant. It was a multicentre, randomized double-blind, placebo- and active-controlled study comparing:

- HTX-011, 400 mg / 12 mg (13.7 mL) administered via instillation (n=58) or HTX-011, 400 mg / 12 mg (13.7 mL) + ropivacaine administered via instillation (n=56) vs saline placebo administered via periarticular injection (n=53) or bupivacaine HCl 0.25%, 125 mg (50 mL) administered via periarticular injection in in adults undergoing total knee arthroplasty (TKA) (n=55).

3.2. Favourable effects

According to the primary analysis for phase 3 studies, Zynrelef (HTX-011), at the doses of bupivacaine 60 mg / meloxicam 1.8 mg and bupivacaine 300 mg/ meloxicam 9 mg, was superior to placebo (primary endpoint) and to bupivacaine HCl (first key secondary endpoint) to manage postoperative pain for 72 hours in bunionectomy and herniorrhaphy measured by mean AUC0-72 of the NRS-A pain intensity scores using wWOCF in the ITT population.

These outcomes were supported by key secondary endpoints showing a reduced opioid consumption and higher proportion of opioid-free subjects over 72 hours. It is estimated that Zynrelef has a clinically significant effect on reduction of pain scores during at least the first 24 hours post-dose and the applicant successfully justified an opioid sparing effect associated with a decrease in ORAE in bunionectomy and herniorrhaphy. This opioid sparing effect of Zynrelef is considered as modest but clinically significant.

The proportion of subjects with severe pain (≥7/10) was significantly reduced in HTX-011 group compared with saline placebo and bupivacaine HCl based on NRS-A (wWOCF, ITT population).

In study 209 in TKA, Zynrelef (HTX-011) bupivacaine 400 mg / meloxicam 12 mg was superior to placebo (mean AUC of NRS-R pain intensity scores using wWOCF in the defined ITT population over 48 hours (primary endpoint) and over 72 hours (key secondary endpoint) compared with saline placebo.

In study 211 in augmentation mammoplasty, HTX-011 400 mg/12 mg, administered as a single dose via nerve block (NB) or via instillation, was superior on the primary endpoint (mean AUC0-24 of the NRS-A pain-intensity scores using wWOCF in mITT Population) compared with saline placebo.

3.3. Uncertainties and limitations about favourable effects

- Studied models in Zynrelef's development programme represent moderate to severe somatic pain model (Bunionectomy study 301, 208; Total knee arthroplasty study 209) and mixed somatic/visceral mild to moderate pain (Herniorrhaphy study 302, 202 and supportive study in Augmentation mammoplasty). There is no provided data on the analgesic effect of HTX-011 in visceral moderate to severe pain models or mixed somatic/visceral moderate to severe pain models, which represents major abdominal, thoracic or vascular surgeries. **Therefore, the originally requested broad indication has been restricted**.
- Uncertainties remain **on the clinical significance of the effect in tested surgeries because the primary endpoint of phase 3 studies is only partially endorsed** in line with the scientific advice, and the minimum difference that would be considered as clinically significant when comparing AUC of pain intensity scores has not been justified.
- In studies 301 and 302 **(bunionectomy and herniorrhaphy)**, it could not be excluded that the effect size on pain (AUC of NRS scores) and decreased opioid consumption on the overall interval (0-72 hours) may be mainly driven by the effects size on the first day post-dose (0-24 hours). In addition, **measure of opioid sparing effect is limited** by study design (no "patient controlled analgesia") and to a lesser extent by the concomitant use of paracetamol rescue medication.
- Phase 2 studies in **total knee arthroplasty (TKA) and augmentation mammoplasty** were not designed or powered to allow a comparison to bupivacaine HCl.
- In **TKA study**, the **primary and key secondary endpoint only considered a comparison against placebo.** Moreover, the **small opioid sparing effect was not associated with a decrease in prespecified ORAEs** and is not considered as clinically significant. **Phase 3 confirmatory results**, including comparison of mean AUC0-72 of pain intensity scores between Zynrelef and bupivacaine HCl as a primary or first key secondary endpoint, would be **necessary to include total knee arthroplasty as a therapeutic indication of Zynrelef.**
- **Augmentation mammoplasty study (211) was an exploratory study where reduction in mean AUC of the NRS-A score through 24 hours (NRS-A0-24; primary endpoint) was showed** for HTX-011 administered via instillation (and via nerve block) **compared with saline placebo. After 24 hours post-dose, there is no clinically meaningful difference in pain scores between HTX-011 400 mg/12 mg and both control groups**. Mean and median total opioid consumption in MME over 72 hours were numerically higher in HTX-011 400 mg/12 mg administered via instillation compared to both control groups. These results are not sufficient to assess B/R in augmentation mammoplasty.

3.4. Unfavourable effects

LAST-related (CV and CNS) depend on the passage of bupivacaine into the bloodstream. Despite the fact that Zynrelef allows to avoid the use of inadvertent intravascular injection and limit bupivacaine systemic exposure, high plasma concentrations of bupivacaine associated with LAST-related TEAEs have been identified and the incidence of certain LAST-related and rapid onset (less than 1 hour) LAST TEAEs is quite similar between HTX-011 and bupivacaine HCl groups. Zynrelef being used in a single administration, the dose cannot be reduced after instillation to better manage AEs.

Impaired healing and local application site TEAEs are of particular interest for this product. Impaired healing was reported with slightly higher incidence in pooled HTX-011 group (2.0% versus 1.5% in bupivacaine HCL and 0.4% in normal saline groups). The risk of local TEAEs and wound healing complications is not dose-dependent but seems to be related to the surgical site and the volume available to instil the product and suturing. In a surgery with a restrictive available amount of space to ensure a complete instillation as bunionectomy, even a reduction of the volume instilled seems not to ensure conclusive results on wound healing complications.

In conclusion, the most important identified risks of Zynrelef are LAST–related symptoms and complications of wound healing in surgery with a small available space to instil the product. Although it seems that the risk of AEs related to systemic exposure to meloxicam is rather low, the possibility of such risk should not be underestimated, especially in specific subpopulations.

3.5. Uncertainties and limitations about unfavourable effects

The safety data emerged from subjects undergoing 4 different surgical procedures (bunionectomy, mammoplasty, herniorrhaphy and TKA), in 4 different surgical sites (2 bony models and 2 soft tissue models) each with its own characteristics (specific anatomic spaces, vascularity, post-surgical level of pain) across heterogeneous populations receiving, for the large majority of the pain medication (opioids and non-opioids "*on demand*" with specific dose regimen for each subject) and with different doses of HTX-011 (ranging from 60mg/1.8mg (bupivacaine meloxicam) to 400mg/12mg). These heterogeneous characteristics represent a limit to draw an accurate conclusion regarding the HTX-011 safety profile.

Safety issues such as LAST and complications of wound healing seems depend on the type of surgery (which could be explained by the different characteristics of each surgical site, i.e. vascularization, space available to instil the product). In the absence of specific studies, it seems difficult to extrapolate the safety profile in other surgical procedures. Hence, the indication was restricted accordingly.

3.6. Effects Table

Table 52: Effects Table for Zynrelef.

Effect	Short Description	Unit	HTX-011	Placebo	Bupivacaine HCL	Uncertainties/ Strength of evidence	References
	Favourable Effects						
Pain relief	Mean AUC_{0-72} of the NRS-A Pain Intensity Scores (SD)	AUC	323.29 (182.641)	445.34 (155.792)	393.5 (153.756)	HTX-011 vs Placebo : -122.05 [-163.76, -80.34], p<0.0001 HTX-011 vs Bupivacaine HCl: -70.16 [-107.07, -33.25], p=0.0022	301: bunionectomy
Pain relief	Mean AUC_{0-72} of the NRS-A Pain Intensity Scores (SD)	AUC	269.39 (173.719)	350.82 (171.224)	341.88 (158.303)	HTX-011 vs Placebo: -81.43 [-125.83, -37.02], p=0.0004 HTX-011 vs Bupivacaine HCl: -72.49 [-108.32, -36.65], p<0.0001	302: Herniorrhaphy
	Unfavourable Effects						

Effect	Short Description	Unit	HTX-011	Placebo	Bupivacaine HCL	Uncertainties/ Strength of evidence	References
TEAEs		%	84,1	81,4	81,4	Safety profile is dependent on the type of surgery. Therefore, pooling of the data has significant limitations.	Phase 2b/Phase 3
LAST	Including Hypotension, Dizziness, Bradycardia, arrhythmia	%	Female 36.0 Male 32.5	Female 30.0 Male 34,4	Female 41,7 Male 44.1		Study 301/302
Wound healing	Including delayed healing, dehiscence	%	2.0	0.4	1.5		Pooled safety data

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Zynrelef has been assessed at different doses and in different types of surgical models (bunionectomy, herniorrhaphy, total knee arthroplasty and augmentation mammoplasty).

Considering the efficacy of the new product in treatment of acute pain the Guideline on the Clinical Development of Medicinal Products Intended for the Treatment of Pain states, that "*The efficacy profile of a new product should normally be established in separate studies for both somatic and visceral nociceptive pain*" and "*to justify a general indication for the treatment of acute pain, efficacy needs to be demonstrated independently in models of both somatic and visceral pain, or in models of somatic pain and mixed somatic/visceral pain*".

In the case of Zynrelef, the **studied models represent moderate to severe somatic pain model** (Bunionectomy study 301, 208; Total knee arthroplasty study 209) **and mixed somatic/visceral mild to moderate pain** (Herniorrhaphy study 302, 202 and supportive study in Augmentation mammoplasty). There is **no data provided** on the analgaesic effect of HTX-011 **in visceral moderate to severe pain models or mixed somatic/visceral moderate to severe pain models,** which represents **major abdominal, thoracic or vascular surgeries**. The applicant argument to replace missing pain models with the mechanism of action of the fixed combination is not endorsed as justification it is based only on an assumption.

The current evidence cannot be extrapolated to pain models not studied (e.g. use in thoracic, large abdominal or vascular surgery) and should be limited to pain models studied in phase 3 (bunionectomy, open inguinal herniorrhaphy) with reasonable extrapolation based on those overall positive phase 3 results.

In **studies 301 and 302 (bunionectomy and herniorrhaphy)**, uncertainties remain **on the clinical significance of the effect in tested surgeries because the primary endpoint of phase 3 studies is only partially endorsed** in line with the scientific advice and the minimum difference that would be considered as clinically significant when comparing AUC of pain intensity scores has not been justified. It should be moreover considered that intrinsic factors with incidence on pain management should be considered across different types of surgery. In addition, it could not be excluded that the effect size on pain (AUC of NRS scores) and decreased opioid consumption on the overall interval (0-72 hours) may be mainly driven by the effects size on the first day post-dose (0-24 hours). **However, it is estimated that Zynrelef has a clinically significant effect on reduction of pain scores during at least the first 24 hours post-dose** and the applicant successfully justified an opioid sparing effect associated with a decrease in ORAE in bunionectomy and herniorrhaphy. **This opioid sparing effect of Zynrelef is considered as modest but clinically significant.**

Overall, Zynrelef's **safety profile is in line with the known safety profile of bupivacaine**, no specific safety issue which can be related to meloxicam was identified. However, the safety profile seems to be **variable depending on the type of surgery and the characteristics of surgical site** (vascularisation, size of the wound and amount of space available for HTX-011). The applicant claimed a broad indication to reduce postoperative pain, but to date, based on safety data reviewed for bunionectomy, mammoplasty, herniorrhaphy and TKA, **the extrapolation of Zynrelef safety to other surgical sites seems difficult to determine**. Hence, the indication was restricted. Furthermore, **two specific concerns remain** to consider as uncertainties.

The first concern is related to the passage of bupivacaine into the bloodstream and compatible with the potential onset of **LAST-related AEs** (CNS and CV). Despite of the fact that Zynrelef allow to avoid the use of inadvertent intravascular injection, the incidence of certain LAST-related AEs is quite similar between Zynrelef and bupivacaine HCl groups (especially in study 302). Regarding LAST-related AEs, higher plasma concentrations of bupivacaine were associated with the highest incidence of LAST-related AEs, but a formal causal relationship between these concentrations and the occurrence of LAST-related AEs remain difficult to demonstrate.

The second concern is related to the administration of an "adequate volume" of the product in the surgical site to ensure both a good **wound closure with no dehiscence and no expression of an excess of Zynrelef from the surgical site**. In a surgery with a restrictive available amount of space for ensure a complete instillation as bunionectomy, even a reduction of the volume instilled seems not ensure conclusive results on the reduction of the major wound healing complications.

3.7.2. Balance of benefits and risks

The benefit/risk balance of Zynrelef is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

NA

3.8. Conclusions

The overall B/R of Zynrelef is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zynrelef is favourable in the following indication:

Zynrelef is indicated for treatment of somatic postoperative pain from small- to medium-sized surgical wounds in adults (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Not applicable

Obligation to conduct post-authorisation measures

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable