Periarticular Bupivacaine + Meloxicam ER Solution Versus Standard Practice During Total Knee Arthroplasty: A single institution, single-blinded, randomized clinical trial

NCT05188053

Document updated 1/29/2024

Document Submitted to PRS 3/4/2025

Periarticular Bupivacaine + Meloxicam ER Solution Versus Standard Practice During Total Knee Arthroplasty: A single institution, single-blinded, randomized clinical trial

Principal Investigator(s) Matthew P. Abdel, M.D.

[Co-Investigator(s)] Harold I. Salmons, M.D.
Dirk R. Larson, M.S.
Robert T. Trousdale, M.D.
Mark W. Pagnano, M.D.
Cory G. Couch, M.D.
Adam W. Amundson, M.D.
Christopher M. Duncan, M.D.
Hugh M. Smith, M.D., PhD.

Department of Orthopedic Surgery

Funding Sponsor: Mayo Clinic
200 First St. SW
Rochester, MN 55905
507-284- 2511

Study Product: bupivacaine +meloxicam ER solution, HTX-011

Protocol Number: (IRBe)

Updated version: [1/29/2024] Version **(2.0)**

Abstract:

Total joint arthroplasty (TJA) remains one of the most prevalent and successful surgical procedures performed on patients seeking return to function from arthritic pain. Effective pain control is critical after surgery to permit earlier mobilization, maximize patient satisfaction, and facilitate outpatient surgery. Multimodal analgesia protocols are the back bone for post-operative functional recovery after TJA, and efforts to optimize these protocols with new FDA approved medications remain of significant importance. The purpose of this study is to examine the efficacy of a recent FDA approved medication: bupivacaine +low dose meloxicam extended release (ER) solution (HTX-011), for post-operative pain control after total knee arthroplasty. This is a 1:1 randomized, single blinded, clinical trial studying this new medication against our institution's standard of care arthroplasty block cocktail. Patients will be randomized by dynamic allocation into treatment and active control groups. The primary outcome of interest is pain control over 72 hours after surgery collected through pain diaries recording an 11-point numeric rating scale (NRS) of 0-10. These scores will be computed as area under the pain curve at 24, 48 and 72 hours, and standardized by daily morphine equivalents required to arrive at our end points. Additional endpoints include distance walked with PT at discharge, , length of stay in the hospital, and adverse events. We hypothesize that this new medication will provide superior analgesia at 72 hours and reduced opioid consumption, in comparison to our current standard of care.

Table of Contents

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IDE	Investigational Device Exemption
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect

Study Summary

Title	**Periarticular bupivacaine + meloxicam ER solution (HTX-011, Zynrelef) Versus Standard Practice During Total Knee Arthroplasty for Perioperative Analgesia: A single institution, single-blinded, randomized clinical trial**
Running Title	Periarticular bupivacaine + meloxicam ER solution vs standard practice during TKA: An RCT
IRB Protocol Number	**21-010044**
Phase	Comparative Study, RCT, single institution, single blind
Methodology	Single blind, randomized, clinical trial; active control (standard practice)
Overall Study Duration	1 year
Subject Participation Duration	72-hours of direct study involvement

Objectives	This study will investigate if bupivacaine +meloxicam ER solution is going to improve patient care at Mayo Clinic through superior and prolonged analgesia following total knee arthroplasty compared to our standard of care.
Number of Subjects	Using preliminary calculations based on the literature, we anticipate enrolling a total of 250 subjects. However, a pilot study will be performed on a total of 10 patients using the exact study medications and methods presented for the formal RCT to more accurately calculate the required sample size. The final sample size for the formal RCT will be based on the results of the pilot study.
Diagnosis and Main Inclusion Criteria	Examination of a new FDA approved extended release bupivacaine +meloxicam solution for periarticular instillation during total knee arthroplasty (TKA) versus institutional standard practice. Inclusion Criteria: Older than 18 years, all genders, presenting for primary total knee replacement for degenerative joint disease and deemed healthy for TKA surgery, patient can provide their own informed consent.
Study Drug	Bupivacaine + meloxicam ER solution, HTX-011 (Zynrelef)- FDA approved for total knee arthroplasty

Duration of Exposure	One time intraoperative dose prior to closure of total knee arthroplasty index procedure
Reference therapy	Mayo clinic standard arthroplasty block : In 100cc of standard formulation, there is 225mg of ropivacaine 5mg/mL, 0.6mg epinephrine 1mg/mL, 30mg ketorolac 30mg/mL diluted in sodium chloride
Statistical Methodology	Area under the curve at 24, 48 and 72 hours will be calculated based on serial numeric rating scale (NRS) pain scores on an 11 point scale with two-sample t-tests for parametric and Wilcoxon rank sum tests for non-parametric data. Dynamic allocation will be used for randomization. Descriptive statistics will be used where appropriate.

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the procedures described in this protocol, applicable United States government regulations and Mayo Clinic policies and procedures.

1.1 Background

Total joint arthroplasty remains one of the most prevalent and successful surgical procedures performed on patients seeking return to function from arthritic pain. Effective pain control is critical after surgery to permit earlier mobilization, maximize patient satisfaction, and facilitate outpatient surgery.

As advancements in medicine and surgery continue to progress, more emphasis is being placed on earlier ambulation following surgery as it has been shown to improve outcomes and decrease hospital length of stay and decrease total cost of care.[1-3]. Optimizing perioperative pain control is crucial to achieving these goals.

Current practice for perioperative pain management during TKA involves the use of multimodal analgesia (MMA). MMA includes multiple oral and IV medications tasked with blocking sensory input around the knee for a period around the indexed surgery[4]. Together, MMA protocols are designed to reduce the need for opioids, decrease postoperative pain intensity and encourage earlier discharges. These effects drive down costs of care. Included with these medications are periarticular injections, which have proven effective in achieving both pain intensity and functional improvement after surgery.[5] While multiple agents have been tested in practice including bupivacaine hydrochloride and ropivacaine as components to MMA protocols, observed effects are often limited to approximately 8 to 12 hours post-operative[6]. More recently, certain bupivacaine liposomal emulsions designed to have prolonged effect have been tested with conflicting evidence reported in their efficacy compared to "shorter acting" substances beyond 24 hours[7]. Thus, continuing to examine new medications and optimize MMA protocols is an important ongoing pursuit both from a quality improvement, patient outcome, and cost effectiveness point of view.

Recently, the FDA approved a new periarticular extended release (ER) solution consisting of low dose meloxicam + bupivacaine for total knee arthroplasty pain control. Their decision is based on the results of a recent Phase 2b clinical trial investigating this drug against standard local periarticular analgesic options.[4] In this Phase 2 clinical trial, 232 patients undergoing primary unilateral total knee arthroplasty under general anesthesia were studied,

and the authors' results ultimately demonstrated that the unique, needle-free, instillation of 400mg bupivacaine/12mg meloxicam ER solution intraarticularly prior to closure provided superior pain reduction out to 72 hours following TKA compared to placebo and active control groups. Bupivacaine + meloxicam ER solution (HTX-011, Zynrelef) is FDA-approved for three specific surgical indications: bunionectomy, herniorrhaphy, and total knee arthroplasty, with the FDA approval stemming from primarily industry involved studies[4,8,9]. Notable benefits included prolonged duration of pain control out to 72 hours postoperative and a concomitant decrease in opioid requirements after surgery[10].

The primary goal of this study is to investigate whether this medication will improve patient care at our institution by conducting the first, non-industry supported, randomized, single-blinded clinical trial comparing bupivacaine + low dose meloxicam ER solution to our institutional standard practice arthroplasty block cocktail during total knee arthroplasty by providing superior analgesia through 72 hours. Our second goal is to evaluate the impact of this medication on patient opioid consumption after surgery and return to ambulation end points in comparison to our standard of care. We hypothesize that this medication will provide improved pain control at 72 hours post-operative resulting in less consumption of opioids and improved ambulation at 72 hours compared to our current standard of care. However, these effects may be associated with a significant increase in cost of care.

Investigational Device

Bupivacaine + low dose meloxicam ER solution (HTX-011) is a recent FDA approved medication used for periarticular instillation to reduce postoperative pain. Bupivacaine + low dose meloxicam ER solution has been approved for bunionectomy, open inguinal

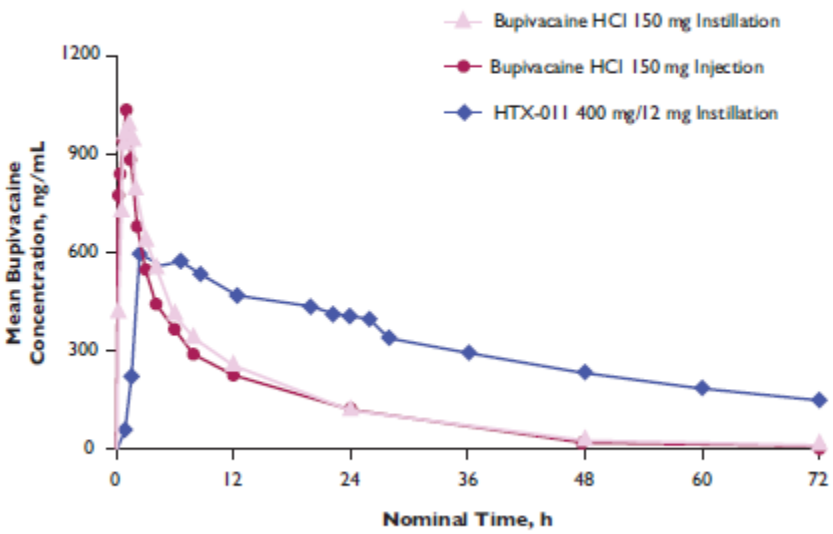
herniorrhaphy, and total knee arthroplasty. Its efficacy has been described out to 72 hours due to a proprietary polymer based formulation with prolonged elusion pharmacokinetics. It is found to be safe, with existing clinical studies suggesting its most common side effects being headache, nausea and constipation[4,8,9].

1.2 Clinical Data to Date

Recently, the FDA approved this new periarticular pain medication, low dose meloxicam + bupivacaine ER solution for total knee arthroplasty pain control, bunionectomy and open inguinal herniorraphy[4,8,9]. For total knee arthroplasty (TKA), this approval decision is based on the results of a recent clinical trial investigating this drug against local periarticular analgesic options (active control) and placebo groups.[4] In that Phase 2 clinical trial, 232 patients undergoing primary unilateral total knee arthroplasty under general anesthesia were studied, and the authors' results ultimately demonstrated that the application of the study drug, 400mg bupivacaine/12mg meloxicam ER solution, intraarticularly prior to closure of a standard TKA midline incision provides superior pain reduction through 72 hours following TKA compared to their placebo or active control groups. The recent FDA approval of this new analgesic medication stemmed from primarily industry involved studies, with notable benefits being prolonged duration of pain control out to 72 hours postoperative and a concomitant decrease in opioid requirements after surgery[10]. Importantly, we asked our pharmacist to critically review the safety of single shot adductor canal blocks, spinal anesthesia, and local skin anesthetic in patients receiving this study medication. Nathaniel Brinkman, Pharm D., RPh, provided a critical analysis of the dosing of this medication, plasma concentrations and

concluded that it is safe to use a single shot adductor canal block plus spinal for patients receiving bupivacaine + low dose meloxicam ER solution. His decision is based on available clinical information which is outlined as follows. Inter-patient variability aside, pertinent data points include a local anesthetic systemic toxicity (LAST) from bupivacaine is thought to occur around 2,000ng/mL. Concentration max for HTX-011 400mg in TKA was 695 ng/mL, which was reached at 21 hours per the package insert. A poster by Yamamoto *et al*. included a range of 368-1,550 ng/mL (mean 710 ng/mL) in *mammoplasty*, i.e. not an intra articular use, which reached max concentration at 3.58 hours (1.27-34.58). Median plasma concentration for combination spinal and single shot femoral blockade was 538 ng/mL (range, 176-1,384 ng/mL)[11]. The theoretical max if all serum concentration maximums were reached at the same time would be 2,079 ng/mL, however the intra articular instillation and prolonged elution of this medication protects against simultaneous serum peak concentrations. This extends to the use of 75 mg bupivacaine as a local skin anesthetic during closure as is the preference of senior author MPA. Local use of bupivacaine in this manner will result in a peak between 200-300 ng/mL at approximately 60 minutes, but the time to peak was identified as variable. Dr. Brinkman expects the combination of spinal anesthesia, adductor blockade and skin infiltration of bupivacaine will have a cumulative peak of 800-900 ng/mL within the 30-120-minute timeframe, well before the bupivacaine +low dose meloxicam ER solution instilled intra articularly peaks, and below the 2,000 ng/mL toxicity threshold.

Figure 1. Mean Plasma Exposure Profiles of Bupivacaine Following Administration of HTX-011 or Bupivacaine HCl



HCl, hydrochloride.

<https://zynrelef.com/pdf/4-Clinical-Evidences/Yamamoto-Pharmacokinetics-Safety-Different-Bupivacaine-Formulations-2019.pdf>

Figure 2. Calculated In Vitro Release Rates of Bupivacaine and Meloxicam From HTX-011 (400 mg bupivacaine/12 mg meloxicam)

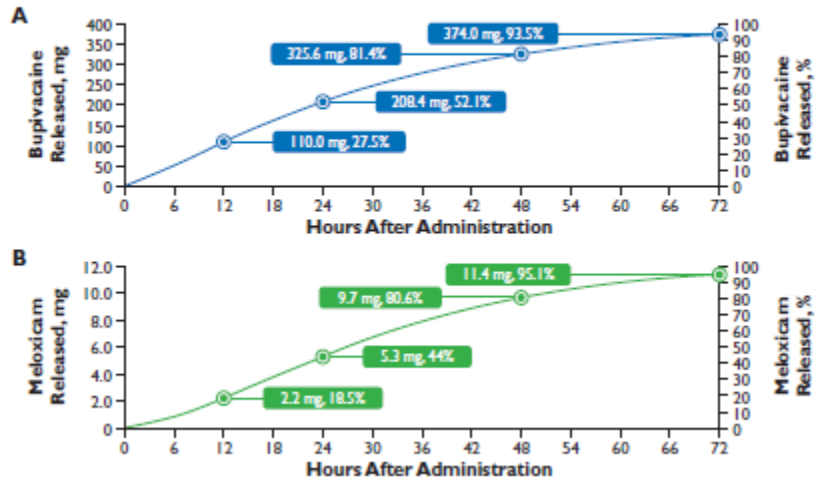


Figure 3. In Vitro Versus In Vivo Release of Bupivacaine and Meloxicam From HTX-011

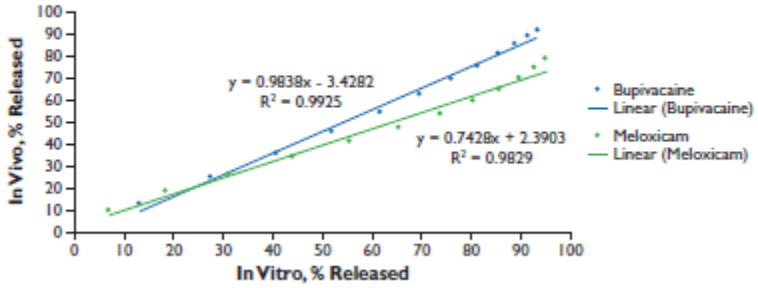
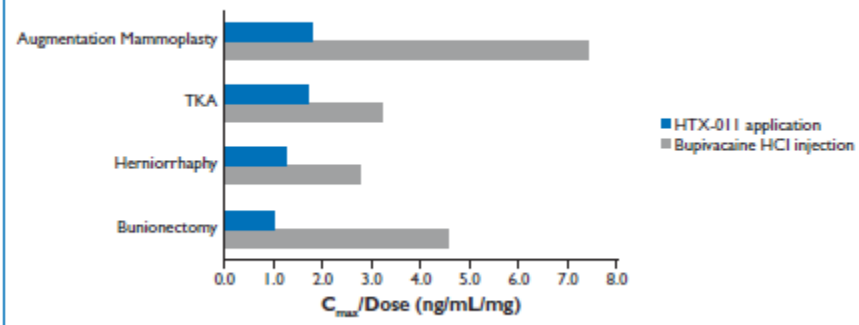


Figure 4. Dose-Normalized C_{max} (C_{max}/Dose) of Bupivacaine Following Administration of Bupivacaine HCl or HTX-011 Across Surgical Procedures



C_{max}, maximum plasma concentration; HCl, hydrochloride; TKA, total knee arthroplasty.

<https://zynrelef.com/pdf/4-Clinical-Evidences/Luke-HTX-011-Predictable-release-rates-2021.pdf>

1.3 Anticipated Duration of the Clinical Investigation

This study is anticipated to be completed within one year of initiation. Each subject will be enrolled for the duration of the study; however, will only require contact over the first 72 hours when they are expected to mail in self-reported pain diaries. They may be contacted by a study coordinator if the diaries are not mailed back to the investigational team.

2 Study Objectives

The overall objective of this study is to investigate whether or not this new FDA approved medication is a viable addition to the Mayo Clinic formulary to improve the quality of patient care following total knee arthroplasty. To this end, we will examine pain at 72 hours as our primary outcome. Secondarily, we will also investigate pain at 48 hours in the study versus control group. Pain at 24 hours will be compared between groups as a tertiary goal, while recognizing that the study medication is reported to differentiate itself through its extended duration of effects. We will collect opioid use information and monitor for standard safety parameters after total knee surgery post-operative. The anticipated duration for complete data collection to analysis is one year.

2.1 Primary Objective

This investigation constitutes a comparative study involving the first non-industry funded investigation of the use of a recently FDA approved periarticular pain medication for controlling postoperative pain following total knee arthroplasty.

Primary Objective

To assess the effectiveness of bupivacaine +meloxicam periarticular ER solution in controlling postoperative pain out to 72 hours in subjects receiving primary total knee arthroplasty compared to standard arthroplasty block controls.

2.2 Secondary Objective

Secondary outcomes will be evaluating pain control at 24 and 48 hours, total post-operative opioid consumption (standardized into MMEs), hospital length of stay, adverse reactions or events, distance walked at time of discharge with PT.

2.1.1 Study Rationale

Based on available literature, periarticular bupivacaine + low dose meloxicam ER solution has been demonstrated as a new and safe means of providing prolonged patient analgesia after total knee arthroplasty. Its novelty is in both its formulation and needle-free instillation. As the available studies to date examining this medication are industry-funded, the primary rationale for examining this FDA approved medication at our institution is to provide an unbiased evaluation of this new medication in the setting of quality improvement initiatives to our institution's patient care. Multimodal analgesia (MMA) is critical to achieving better outcomes after total joint arthroplasty, as it has been shown to decrease hospital length of stay through earlier ambulation and patient satisfaction. It also has the benefit of reducing narcotic consumption postoperatively. Continuing to evaluate optimal protocols and new medications for MMA consideration remains of significant value.

Various means of controlling post-operative pain are currently employed at Mayo Clinic. Standard arthroplasty block is a cocktail of multiple medications instilled with a needle prior to closure of total knee arthroplasties. In 100cc of our current formulation, there is 225mg of ropivacaine 5mg/mL, 0.6mg epinephrine 1mg/mL, 30mg ketorolac 30mg/mL diluted in sodium chloride. While effective at controlling patients' pain intensity postoperatively, ropivacaine's post-operative analgesic effects are recognized to last for less than 24 hours. As

the pain following total knee arthroplasty experienced by a patient can be quite limiting at first, continuing to evaluate MMA protocols using new, FDA approved medications remains of significant value.

An essential component to a new drug reaching FDA approval is an analysis of not only the drug's efficacy but also its safety profile. Bupivacaine + low dose meloxicam ER solution has been shown through multiple large clinical trials to be safe with its most common adverse effects reported as constipation, nausea and headache[4,8,9].

2.1.2 Anticipated Risks

The existing evidence on this new FDA approved medication suggests that it is safe. The adverse effects with >/= 10% incidence that have been reported are constipation, vomiting and headache. This is a single one-time intra articular dose of this medication. As such, the standard risks of intravenous instillation of local analgesics such as bupivacaine (cardiotoxicity) and meloxicam (renal, GI, bleeding and cardiovascular toxicity) are likely mitigated by the local instillation and one-time dose. Further, following thorough discussion with on staff pharmacy expert, Nathaniel Brinkman, Pharm D, the elution kinetics of this medication outlined in the available literature does not show brisk accumulation in serum given the local instillation and prolonged elution kinetics of the medication as detailed above in section 1.2. Thus, the drug is considered safe with adjuvant neural blockade such as spinal anesthesia, single shot adductor canal block and local anesthetic instillation to skin during

closure. Given the ingredients of this medication, the list of possible risks and adverse effects includes:

- Hypersensitivity/ allergic response
- Hypertension
- Renal toxicity
- Cardiac toxicity
- Hepatotoxicity/transaminitis
- Methemoglobinemia
- Heart failure and edema
- Prolongation of postoperative bleeding
- Drug-drug interactions with other NSAIDs, hemostasis interfering medications (e.g. warfarin, aspirin, SSRI/SNRIs)

There are also risks associated with the index surgery which are explained to every patient during their informed consent for surgery. These risks include:

- Death
- Fever
- Infection
- Damage to surrounding neurovascular or ligamentous structures during surgery
- Stroke
- Wound complications
- Deep venous thrombosis or Pulmonary embolism

- Fracture and subsequent surgeries

2.1.3 Potential Benefits

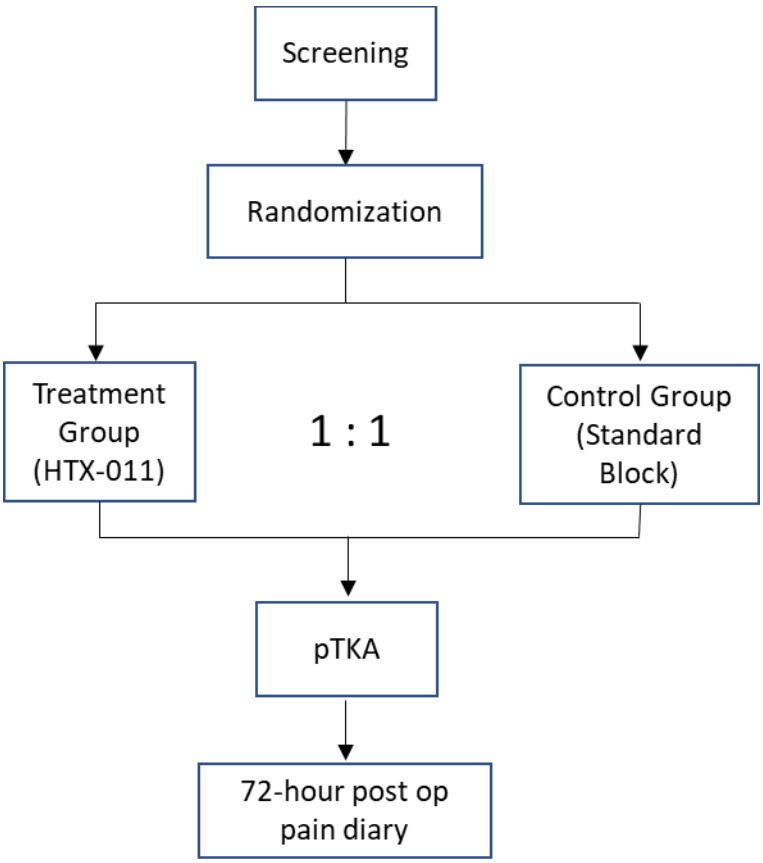
The anticipated benefit of this study will be identifying the effectiveness of a new FDA approved periarticular analgesic in a non-industry sponsored cohort of subjects receiving total knee arthroplasty at a single high-volume orthopedic hospital. This information will inform clinical practice through quality improvement initiatives as it may prove worthwhile to be incorporated into existing MMA protocols at our hospital. There is a proposed advantage of this medication having a 72 hour analgesic effect with an associated reduction in opioid requirements.

3 Study Design

3.1 General Design

- Randomized, single-blinded, standard of care group as a control, single institution, clinical trial
- 72 hours direct patient study involvement may be contacted out to the point of publication for general follow-up.
- Patients will be recruited for the study at their preoperative appointments. They will be randomized using a computer algorithm with dynamic allocation. They will not be informed as to their study group. They will receive their scheduled pTKA. They will follow up with their pain diaries over the subsequent 72-hours after which time they will return them to the investigational team with pre-paid postage.

- There is no long term follow up outside of their normal scheduled post-operative visits with their surgeon to monitor their progress with surgical recovery. Primary and secondary endpoints will be observed and collected over the first 72 hours after surgery.



3.2 Primary Study Endpoints

Mean patient reported (0-10) numeric rating scale (NRS) pain scores area under the curve (AUC) at 72 hours adjusted for opioid consumption.

3.3 Secondary Study Endpoints

Secondary outcomes will be mean patient reported (0-10) NRS pain scores area under the curve (AUC) at 24 and 48 hours postoperative, total post-operative opioid consumption (standardized into MMEs), hospital length of stay, adverse reactions or events, and distance walked with PT prior to discharge.

3.4 Primary Safety Endpoints

This is an FDA approved medication for the present indication. It is not investigational in this setting but is rather being evaluated for quality improvement of patient care at Mayo Clinic. As such, standard post-operative evaluation for patients who have received total joint arthroplasty will be utilized. This will include serial neurovascular examinations and notation of any complications including but not limited to unexpected ICU admissions, prolonged hospitalizations, venous thromboembolic disease, wound problems and drug hypersensitivity reactions.

4 Subject Selection, Enrollment and Withdrawal

Consecutive adults greater than the age of 18 years old who have consented for this study and are receiving primary total knee arthroplasty to treat degenerative joint disease are qualified for inclusion. These subjects must all be deemed healthy for surgery (American Society of Anesthesiologists (ASA) physical classification I to III) will be included in this randomized, controlled trial as this simulates our clinical practice population. We will exclude patients with contraindications to NSAIDs or bupivacaine including allergies (Type 1

hypersensitivity) and severe renal disease. We aim to represent a standard patient population receiving total joint arthroplasty at our institution.

4.1 Inclusion Criteria

- ASA classification I to III older than or equal to 18 years old
- All genders
- Presenting for primary total knee replacement for degenerative joint disease
- Patient capable of providing their own informed consent

4.2 Exclusion Criteria

- Vulnerable study populations including prisoners
- Patients with a contralateral total knee arthroplasty <2 years prior to the index procedure
- Compromised health barring the patient from proceeding with surgery
- Patients unable to provide their own informed consent
- Pregnancy
- Patients with documented chronic pain syndromes
- Patients with a history of prolonged daily opioids (more than 1 month) with an oral morphine equivalent of greater than 5mg/day
- BMI >45 kg/m^2

- Type I hypersensitivity to any component of the study medications
- Patients with impaired cognitive function inhibiting ability to provide informed consent
- Severe renal (estimated glomerular filtration rate less than 50ml/min))

4.3 Subject Recruitment, Enrollment and Screening

Subjects will be identified as those who meet the inclusion criteria and are receiving total knee arthroplasty for degenerative joint disease from the clinical practices of participating high-volume adult reconstruction surgeons at the Mayo Clinic that have agreed to participate in our study. We will recruit patients at their pre-operative visit, where they will be screened for exclusion/inclusion criteria and enrolled by a trained research coordinator at the time of consent for surgery. We anticipate 25 eligible patients seen in an average month, and assume that 70% of patients will agree to participate. While there should be no loss to follow-up in this study (due to the short nature of the follow-up), we assume that up to 10% of subjects will not complete or return their pain diaries. Thus, we expect that there will be 15 patients enrolled with complete data per month. Preliminary sample size calculations (section 7.1) were based on previously published data. However, because of differences in the intervention and follow-up protocol in this proposed RCT, a pilot study of 10 patients following this same protocol using this on-formulary medication will be conducted in a single author (MPA's) clinical practice. Five patients will receive HTX-011 and the other 5 patients will receive the standard practice pain block. The data from this pilot study will be used to refine the initial sample size estimate and will provide the final sample size determination for the RCT. However, the data from the pilot study will not be included in the full RCT analysis. The

other advantage of the pilot study is that it will provide study personnel an opportunity to become familiar with the procedures and flow of subject enrollment and data collection prior to the initiation of the actual RCT. The informed consent document will contain information about the study drug (benefits and safety information), the importance of the study, and the contact information of the investigative team for any questions. At that time, the pain diary will be shown to them with specific education provided by the coordinator as to how to use the diary (a second round of education will occur on the day of surgery when the patient is done with their surgery at which time the diary will be provided to them by the coordinator). The coordinator will screen patients for inclusion/exclusion criterion and confirm selection of any patient that they have questions. The coordinator will also remind patients of how to use the diary throughout their 3-day postoperative period through reminder patient portal messages organized through Mayo Clinic. Patients will not be notified which treatment arm of the study they fall into as this is a single blind, randomized, controlled trial. Given the novel needle-free application of this medication compared to the active standard arthroplasty block control group (injection), the surgeons will not be blinded to treatment allocation, however the surgeons will not collect postoperative patient reported outcomes from the patient, who themselves will be blinded. Nurses who take care of the patients in the hospital and assist them in their initial pain diary recording will be blinded to the treatment allocation.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Study procedures include index TKA at which time the medication of interest will be administered. Subjects will then be asked to complete pain diaries using numerical rating scale (NRS) pain scores on an 11 point scale (0-10) for 72 hours while also tracking their opioid consumption. They will then return the diary to the investigators and their direct involvement will be complete. It is not anticipated to withdraw a qualified and consented subject for any reason except if they fail to complete and return the pain diary. If that happens, they will be replaced if insufficient data is provided for primary end point calculations.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Not applicable. No long term follows up is being pursued for this study.

5 Study Device

Bupivacaine + low dose meloxicam ER solution is a recent FDA approved medication used for periarticular instillation to reduce postoperative pain. Bupivacaine + low dose meloxicam ER solution has been approved for bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty based on recent studies[4,8,9]. Its efficacy has been described out to 72 hours due to a proprietary polymer design with prolonged drug elusion pharmacokinetics. Bupivacaine exerts its analgesic effect by preventing cell membrane depolarization through blocking sodium ion influx into sensory neurons. Meloxicam is a non-steroidal anti-inflammatory medication (NSAID) which exerts its effect through blockade of

cyclooxygenase enzymes and subsequent down regulation of pro inflammatory prostaglandin mediators. This combination medication is shown to be safe, with existing clinical studies suggesting its most common side effects are headache, nausea and constipation (incidence >/=10%)[4,8-10]. The device will be obtained through its manufacturer and will be received as a sterile unopened medication to be administered during surgery in standard sterile fashion.

Description

Bupivacaine + low dose meloxicam ER solution is a recent FDA approved medication used for periarticular instillation to reduce postoperative pain. Bupivacaine + low dose meloxicam ER solution has been approved for bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty. Its efficacy has been described out to 72 hours due to a proprietary polymer design with prolonged elusion pharmacokinetics of its two primary ingredient reagents. The drug has been designed and manufactured by Heron Therapeutics (Heron Therapeutics, San Diego, CA) for use as a multimodal analgesic local analgesic during surgery. This medication was recently approved for formulary status in TKA at Mayo Clinic. Traceability will be maintained through standard institutional practice for formulary drugs administered during a patient's hospitalization. The specific purpose of the use of this medication in this study is to evaluate whether it provides superior analgesia for 72 hours in comparison to our standard of care. This quality improvement initiative seeks to augment the care of our patients while concomitantly evaluating a new FDA approved medication in a non-industry sponsored randomized controlled trial for this purpose. This device will be used in patients who have consented for this research and do not have contraindications to receiving this medication during their indexed primary total knee arthroplasty. The goal is to

reflect our standard practice and observe whether this medication improves patient care. The drug is administered through a novel needle-free instillation into the joint prior to closure, as described in the drug manual. No specific training outside of knowledge of the user manual for the medication is required.

5.1 Method for Assigning Subjects to Treatment Groups

A study coordinator will handle subject screening, recruitment, and informed consent in a patient's preoperative appointment for indexed primary total knee arthroplasty. Upon enrollment, study patients will be assigned to the available study number.
Subjects will be randomized into one of two study groups using dynamic allocation. To ensure the study groups are balanced on subject demographics, the subjects will be stratified on sex, age group (≥70 vs. <70), and BMI (≥32 vs. <32). Within each stratum, subjects will be assigned to either of the two study groups using a computerized dynamic allocation program housed in an online application developed by personnel in the Division of Clinical Trials and Biostatistics. Using dynamic allocation will ensure that the subject allocation will remain balanced on the stratification factors and the study group assignment throughout the entire subject accrual phase. This computer-based randomization system will be username and password protected and available only to the study personnel. The study group assignment will be concealed from the patient in this single-blind study, as the surgeon will instill the medication intraoperatively and cannot be blinded to it given its unique method of needle-free administration.

5.2 Preparation and Administration/Implantation of Investigational Device

Bupivacaine +meloxicam ER formulation is intended for single dose administration only. The drug is applied without a needle into the surgical site following final irrigation and suction and prior to suturing. The recommended dose that we will incorporate is 14cc to deliver 400mg bupivacaine/12mg meloxicam. Following standard sterile practice, the prepackaged, sterile medication kit will be brought to the surgical field for instillation prior to closure. The medication is a viscous solution supplied as a kit consisting of single dose glass vial and the following sterile components: Luer Lock syringe, a vented vial spike, Luer Lock cone-shaped applicator(s) and syringe tip cap(s). Per the manufacturer's complete prescribing information materials, the contents of the drug vial are sterile. The vial exterior is not sterile. We will follow standard institutional practice to sterilely prepare and administer this medication for surgery.

For the control/standard of care group receiving our standard arthroplasty block cocktail, the surgeon will instill the medication as an injectate into the posterior capsule, and soft tissues, during closure.

Per the manufacturer guidelines, the complete steps to prepare the medication are the following: https://www.zynrelef.com/prescribing-information.pdf

1. ZYNRELEF is a clear, pale yellow to yellow, viscous liquid. Visually inspect the ZYNRELEF vial for particulate matter and discoloration. Obtain a new vial if particulate matter or discoloration is observed.
2. Prepare vial for filling of syringe(s) by attaching vented vial spike. Prepare syringe by filling with air then attach to vented vial spike.
3. Invert to allow product to fill the vial neck and push air into vial. Withdraw dose of ZYNRELEF into syringe. (The dose volume takes into account the potential residual volume in the components.)

Nominal Dose of Bupivacaine / Meloxicam (mg/mg)	Number of Syringes and LLAs* Per Dose	Volume to be Withdrawn (mL)
60 / 1.8	1	2.3 (using 3 mL syringe provided)
200 / 6	1	7 (using 12 mL syringe provided)
300 / 9	1	10.5 (using 12 mL syringe provided)
400 / 12	2	14 (using two 12 mL syringes provided, 7 mL ZYNRELEF per syringe)

*LLA: Luer lock cone-shaped applicator

4. Repeat steps 1-3 for more than one syringe.
5. Prepare product immediately prior to use and apply syringe tip cap until product delivery.

5.3 Subject Compliance Monitoring

Subjects are only required to complete and return pain diaries after surgery. Subjects who do not return a pain diary within 1 week after surgery will be contacted by the study coordinator. If a pain diary is never recovered that subject will require exclusion so as to avoid recall bias of delayed diary completion.

5.4 Prior and Concomitant Therapy

Subjects will receive perioperative analgesia, regardless of treatment group, with our standardized institutional Multimodal Analgesia Total Joint Pathway consisting of immediate or controlled-release oxycodone, celecoxib and acetaminophen, unless contraindicated. Intraoperative management will include the primary anesthesia type (which will be standardized to spinal anesthesia with a single adductor canal block consisting of 0.25% bupivacaine +/- epinephrine 10cc total, as deemed safe by the treating anesthesiologist), antiemetics, and supplemental analgesia as deemed necessary. No patients will receive Precedex, which is otherwise considered at the physician's discretion as a component to MMA pathways at Mayo Clinic. All patients will receive a posterior stabilized (PS) total knee arthroplasty through a medial parapatellar approach, and all procedures will be performed by high-volume, lower-extremity arthroplasty surgeons at the Mayo Clinic Hospital, Methodist Campus in Rochester, Minnesota.

5.5 Packaging and Labeling

This is an FDA approved pharmaceutical being evaluated as a quality improvement initiative against our institution's current standard of care. Its label will be that which is provided through standard purchasing by the formulary team at Mayo Clinic Methodist Hospital from the manufacturer, Heron Therapeutics (San Diego, CA).

5.6 Masking/Blinding of Study

A study coordinator will handle subject recruitment and informed consent in a patient's preoperative appointment for indexed primary total knee arthroplasty. Upon enrollment, study patients will be assigned to an available study number. Subjects will be randomized into one of two study groups using dynamic allocation. To ensure the study groups are balanced on subject demographics, the subjects will be stratified on sex, age group (≥70 vs. <70), and BMI (≥32 vs. <32). Within each stratum, subjects will be assigned to either of the two study groups using a computerized dynamic allocation program housed in an online application developed by personnel in the Division of Clinical Trials and Biostatistics. Using dynamic allocation will ensure that the subject allocation will remain balanced on the stratification factors and the study group assignment throughout the entire subject accrual phase. This computer-based randomization system will be username and password protected and available only to the study personnel. The randomization assignment will be concealed from the patient in this single blind study, as the surgeon will instill the medication intraoperatively and cannot be blinded to it given its unique method of needle-free administration.

5.7 Receiving, Storage, Distribution and Return

5.7.1 Receipt of Investigational Devices

This is not an investigational device. It is on formulary at Mayo Clinic and will be available through the pharmacy for total knee replacement surgery.

5.7.2 Storage

This medication should be stored at room temperature (20 deg C to 25 deg C. Once vials are removed from the kit, they must be stored at controlled room temperature protected from light.

5.7.3 Distribution of Study Device

The device will be instilled intraoperatively as a onetime dose in patients randomized to the treatment group.

5.7.4 Return or Destruction of Study Device

Not applicable.

5.7.5 Cleaning/Sterilization Procedures (optional)

Not applicable.

6 Study Procedures

6.1 Entire study visit

	Schedule of Events		
Study Activity	**Pre operative Appointment**	**Index Surgery**	**Post Operative**

			(>72 hours)
Identification and Screening	X		
Consent	X		
History	X		
Physical Exam/ review of radiographs	X	X	
Case Report Forms	X	X	
+/- Preoperative health visit (POE, PAME, etc)	X		
Collection of pain diary by pre paid mail in postage (Study Coordinator to Assist)			X

The endpoint of pain out to 72 hours will be assessed by asking patients to record pain scores on a 11-point (0-10) scale every four hours after surgery beginning POD 1 at 8AM in a pain diary. The pain diary set up is designed to replicate standard nursing pain score measurement intervals following surgery, to ensure continuity of pain scores and ease of collection. The NRS selected for this study is designed to mimic the standard orthopedic nursing pain scales used while a patient is in the hospital. POD 0 pain scores will be collected for each patient from the medical record following standard nursing practice at our institution including early post-operative assessment within one hour on arrival to the PACU, and then gradually increased intervals until q4hour standard checks are reached for outpatients in a bed and inpatients. Additional outcome measures include opioid consumption during and after hospitalization converted to daily oral morphine equivalents documented by either anesthesia or the orthopedic nursing staff while patients are inpatient, and then through the patient's

pain diary (#pills and dose per pill) once they leave the hospital. Hospital length of stay will also be noted. After 72 hours post-operative, patients will be instructed to return their pain diaries to the investigating team using pre-paid, pre stamped postage from which data will be recorded by the study coordinator.

Standard monitoring for adverse events after total knee arthroplasty will be utilized. This includes monitoring for patient falls while hospitalized, nerve injury through routine neurovascular exams, surgical site infection through physical examination or unanticipated intensive care unit admissions and drug hypersensitivity reactions.

7 Statistical Plan

7.1 Sample Size Determination

It has been shown that a reduction of 30% in NRS pain scores is associated with a meaningful benefit[12]. Therefore, sample size calculations were performed to estimate the number of subjects needed to detect a difference of this magnitude or greater between the two study groups. In a similar study[4], patients undergoing total knee arthroplasty (TKA) that received HTX-011 + ropivacaine had a mean area under the curve (AUC) pain score from 0 to 72 hours of 452.5 with a standard deviation of 194.1. A difference of 136 represents a 30% change relative to 452.5. Enrollment of 250 subjects is anticipated to allow for subject non-compliance with completing or returning the diaries. However, assuming similar variability is observed in the above proposed study, only 44 subjects with completed diaries per group (88 total) will be required to have 90% power to detect a difference of at least 136 in the AUC of NRS pain scores from 0 to 72 hours between the two study groups.

To more accurately estimate the required study sample size, a small pilot study will be conducted to refine the above estimates. The study PI (MPA) will randomize 10 patients from his practice scheduled for primary TKA to either the study medication (n=5) or the standard medication (n=5). The medications used, procedures followed, and data collected will be identical to those outlined for the full RCT. The data from this pilot study will be used to refine the initial sample size estimate and will provide the final sample size determination for the RCT. However, the data from the pilot study will not be included in the full RCT analysis.

7.2 Statistical Methods

All statistics for this randomized controlled trial will be performed by senior statistician, Dirk Larson, M.S. who has developed and approved the following statistical plan. The data will be reported descriptively using appropriate summary statistics, including means and standard deviations for continuous variables and counts and percentages for categorical variables. Where appropriate, outcomes will be reported with 95% confidence intervals. Because this is a prospective, randomized trial, no formal between-group comparisons of baseline covariates will be performed. The primary study outcome will be patient reported pain over 72 hours following total knee arthroplasty. Patients will record their pain on an 11-point scale (0-10 numerical rating scale, NRS) at specified intervals over the 72-hour period. For each patient, these pain scores will be used calculate the area under the curve (AUC) representing a single measure of pain experienced over the 72-hour period[4,13]. The AUC will be calculated using the trapezoid rule[14]. Secondary outcomes will include the AUC for pain over the first 24 and 48 hours, maximum pain reported, total post-operative opioid consumption (standardized into

MMEs), hospital length of stay, adverse reactions or events, distance walked with physical therapist prior to discharge. Outcomes measured on a continuous scale will be compared between the 2 study groups using two-sample t-tests if the data are sufficiently normally distributed; otherwise non-parametric Wilcoxon rank sum tests will be used. Ordinal variables will be analyzed using non- parametric Wilcoxon rank sum tests. Binary and nominal categorical outcomes will be compared between the study groups using chi-square tests or Fisher's exact tests, if low expected cell counts are observed. Analysis of the primary outcome ($AUC_{0\text{-}72}$) will be analyzed both with and without accounting for the need for opioid rescue medication. The former will be performed by substituting NRS pain scores during opioid rescue medication usage with the most recent NRS pain value prior to the time of opioid rescue medication use[4]. Since this is a prospective, randomized trial, subjects in the two groups are expected to be similar with respect to their baseline characteristics; therefore, no formal comparisons of baseline data will be performed. However, if it is determined that an adjusted analysis is warranted, this will be done using a general linear models framework. The primary analysis will be conducted using an intent-to-treat approach in which subjects will be analyzed in the groups they were randomized to, even if they actually received the intervention for the other study group. All statistical tests will be two-sided, and the threshold of statistical significance will be set at $\alpha = 0.05$.

Handling of Missing Data

If a subject's pain diary is missing a recording of their pain level or opioid consumption at a particular four hour time point after POD 1, we will assess the quality of the rest of the data provided. If sufficient data is deemed available for inclusion, missing NRS pain scores will

be imputed using the last observation carried forward approach. Missing opioid consumption data will not be imputed. If insufficient data is presented the subject will be excluded from the analysis. A sensitivity analysis will be conducted by performing the analysis of the primary outcome after excluding any subjects for whom any NRS pain scores were imputed.

Multiplicity

Given the study design and outcome definitions, multiplicity will not be an issue. The serial NRS pain scores will be converted into a single measure of pain as the area under the curve (AUC) over the 72-hour period. All other outcomes will also be recorded as a single value for each subject. The analysis will entail comparison of the outcomes between the two study groups. Therefore, there will be no analyses involving multiple comparisons.

Primary Hypothesis:

The primary research hypothesis is that subjects randomized to bupivacaine + meloxicam ER solution instilled periarticular at the time of total knee arthroplasty will have superior analgesia over the first 72 hours post-surgery compared to subjects randomized to standard arthroplasty block.

This hypothesis will be tested by comparing the area under the curve (AUC) for numerical rating scale (NRS) of pain over the first 72 hours following surgery between the two study groups using two-sample t-tests if the data are sufficiently normally distributed, or non-parametric Wilcoxon rank sum tests if a high degree of non-normality is observed. The primary analysis will be conducted using an intent-to-treat approach in which subjects will be

analyzed in the groups they were randomized to, even if they actually received the intervention for the other study group. A secondary per-protocol analysis may also be performed.

Secondary Hypothesis:

The secondary research hypotheses include the following.

- Subjects randomized to HTX-011 will have lower mean NRS pain score area under the curve from 0 to 48 hours post-surgery compared to subjects randomized to the standard arthroplasty block.
- Subjects randomized to HTX-011 will have lower opioid consumption in the 72 hours post-surgery compared to subjects randomized to the standard arthroplasty block.
- Subjects randomized to HTX-011 will be able to walk farther - prior to discharge than subjects randomized to the standard arthroplasty block.

The secondary hypotheses will be compared between the two study groups using two-sample t-tests; however, if the data are not sufficiently normally distributed for any of these outcomes, the comparisons will be performed using non-parametric Wilcoxon rank sum tests.

Interim Analysis

Inasmuch as patient accrual is expected to be rapid and the study follow-up period is only 3 days post-surgery, an interim analysis is not likely to be beneficial. Therefore, no interim analysis will be performed.

7.3 Subject Population(s) for Analysis

All subjects randomized into this study, in either the treatment or standard of care group will enter this analysis. Thus, the primary analysis will be performed using an intent-to-treat approach. It is not anticipated that many patients will receive a different intervention than the one they are randomized to, but if this is the case, a secondary analysis may be performed using a per-protocol approach.

8 Safety and Adverse Events

All adverse events occurring during the study, including those not meeting the criteria of an Unanticipated Adverse Device Effect (UADE) will be recorded. Records of these events will be maintained and reports submitted to the IRB according to the regulatory requirements. Expected clinical adverse events and nonsignificant (not serious) clinical adverse events will not be reported. Expected clinical adverse events and anticipated adverse device effects are those listed in Section 1.5.2.

8.1 Definitions

Unanticipated Adverse Device Effect (UADE)

A UADE is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or

IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Adverse Effect (Event)

Any untoward medical occurrence in a subject involved in clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study related treatment(s).

Associated with the investigational device: There is a reasonable possibility that the adverse effect may have been caused by the investigational device.

Life-threatening adverse effect: Any adverse effect that places the subject, in the view of either the investigator or the sponsor, at immediate risk of death from the effect **as it occurred**. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse effect: An adverse effect is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- death
- a life-threatening AE
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity

- a congenital anomaly/birth defect.

Unanticipated adverse effect: Any adverse effect, the nature, specificity, severity, or frequency of which is not consistent with the risk information in the clinical study protocol or elsewhere in the current IDE application.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event will also be recorded and documented as an adverse event.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as an unanticipated adverse device effect unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition.

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Post-study Adverse Event

Patients will follow up with their surgeon at standard intervals specific to their surgeons' preference and the patient's medical condition. If adverse events are identified, patients will be followed by their primary health care team.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets all of the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new

information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**

- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event Reporting Period

Adverse events associated with the study drug will be assessed as those events that have transpired during the 72 hour window following surgery.

8.2 Recording of Adverse Events

No additional measures to collect adverse event information outside of 72 hours from surgery will be collected for this FDA approved medication. Patients will follow up with their treatment team as needed or as part of their consulting surgeons' respective follow up

protocols. This medication is not investigational. It is FDA approved for TKA with expected analgesic effects out to 72 hours post-operative.

8.3 Sponsor-Investigator Reporting of Unanticipated Adverse Device Effects and Unanticipated Problems

Not applicable to this FDA approved, on formulary medication. This is a quality improvement study assessing if this drug is superior to our current institutional practices.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data comprise all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.

9.3 Case Report Forms

A Case Report Form (CRF) will be completed for each subject enrolled into the clinical study. The investigator-sponsor will review, approve and sign/date each completed CRF; the investigator-sponsor's signature serving as attestation of the investigator-sponsor's

responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

Data Management

Data will be compiled into a secure and password protected datasheet file for electronic storage. Study numbers will be assigned to each subject.

Data Processing

Data will flow from the coordinator who collects the pain diaries to the study investigators to Dirk Larson for analysis.

Data Security and Confidentiality

Patient study numbers will be assigned and they will be deidentified thereafter. A secure datasheet file will be used to store their information and endpoints will be updated after receipt of their pain diaries which may be associated with their patient ID number that is unique to them within the study.

Data Clarification Process

Not applicable

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports during the study and for the longer of the following;

1. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The sponsor-investigator will permit study-related monitoring, audits, and inspections by the IRB, the monitor, and government regulatory agencies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The

sponsor-investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as a sponsor-investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed and dated by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

This study will be financed through a patient's individual insurance to cover their surgery and course of care. Additional study fees will be incurred by funds that are supervised by Dr. Matthew P. Abdel.

Conflict of Interest

No member of the investigative team has a conflict of interest to disclose pertaining to this study drug of interest.

13 Publication Plan

Dr. Salmons and Dr. Abdel will oversee all phases of this study leading to its publication. They will be responsible for ensuring the results are published. This study will be registered on Mayo Clinic's clinical trial's website prior to subject recruitment and enrollment. Results will be posted within 12 months of final data collection for the primary outcome.

14 References

1. Guerra ML, Singh PJ, Taylor NF. Early mobilization of patients who have had a hip or knee joint replacement reduces length of stay in hospital: a systematic review. *Clin Rehabil.* 2015;29(9):844-854.
2. Yakkanti RR, Miller AJ, Smith LS, Feher AW, Mont MA, Malkani AL. Impact of early mobilization on length of stay after primary total knee arthroplasty. *Ann Transl Med.* 2019;7(4):69.
3. Molloy IB, Martin BI, Moschetti WE, Jevsevar DS. Effects of the Length of Stay on the Cost of Total Knee and Total Hip Arthroplasty from 2002 to 2013. *J Bone Joint Surg Am.* 2017;99(5):402-407.
4. Lachiewicz PF, Lee GC, Pollak RA, Leiman DG, Hu J, Sah AP. HTX-011 Reduced Pain and Opioid Use After Primary Total Knee Arthroplasty: Results of a Randomized Phase 2b Trial. *J Arthroplasty.* 2020;35(10):2843-2851.
5. Martin NJ, Padmanabhan V, Pindis JJ. Efficacy of Periarticular Cocktail Injection in Rheumatoid Patients Undergoing Total Knee Replacement. *Indian J Orthop.* 2020;54(6):811-822.
6. Yuenyongviwat V, Pornrattanamaneewong C, Chinachoti T, Chareancholvanich K. Periarticular injection with bupivacaine for postoperative pain control in total knee replacement: a prospective randomized double-blind controlled trial. *Adv Orthop.* 2012;2012:107309.
7. Hyland SJ, Deliberato DG, Fada RA, Romanelli MJ, Collins CL, Wasielewski RC. Liposomal Bupivacaine Versus Standard Periarticular Injection in Total Knee Arthroplasty With Regional Anesthesia: A Prospective Randomized Controlled Trial. *J Arthroplasty.* 2019;34(3):488-494.
8. Viscusi E, Gimbel JS, Pollack RA, Hu J, Lee GC. HTX-011 reduced pain intensity and opioid consumption versus bupivacaine HCl in bunionectomy: phase III results from the randomized EPOCH 1 study. *Reg Anesth Pain Med.* 2019.
9. Viscusi E, Minkowitz H, Winkle P, Ramamoorthy S, Hu J, Singla N. HTX-011 reduced pain intensity and opioid consumption versus bupivacaine HCl in herniorrhaphy: results from the phase 3 EPOCH 2 study. *Hernia.* 2019;23(6):1071-1080.
10. Singla N, Winkle P, Bertoch T, Hu J, Beaton A, Redan J. Opioid-free recovery after herniorrhaphy with HTX-011 as the foundation of a multimodal analgesic regimen. *Surgery.* 2020;168(5):915-920.
11. Lapmahapaisan S, Chinachoti T, Kongpatanakul S, et al. Plasma concentrations of bupivacaine after spinal anesthesia with single shot femoral nerve block in total knee arthroplasty. *J Med Assoc Thai.* 2013;96(3):312-317.
12. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain.* 2008;9(2):105-121.
13. Mont MA, Beaver WB, Dysart SH, Barrington JW, Del Gaizo DJ. Local Infiltration Analgesia With Liposomal Bupivacaine Improves Pain Scores and Reduces Opioid Use After Total Knee Arthroplasty: Results of a Randomized Controlled Trial. *J Arthroplasty.* 2018;33(1):90-96.
14. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *Bmj.* 1990;300(6719):230-235.

15 Attachments