Title: Analysis of hydrocodone compared to acetaminophen and ibuprofen for post-nail procedure analgesia

NCT #: NCT05544734

Version Date: 08/15/2022

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IRB Protocol #: 21-10024054
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Statement of Compliance

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

‡ United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM, unless disclosure on ClinicalTrials.gov is federally required.

List of Abbreviations

WCM	Weill Cornell Medicine
PGIA	Physician Global Improvement Score
PGA	Physician Global Assessment
AE	Adverse events
ADE	Adverse Device Effect
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect

1. Protocol Summary

Full Title:	Analysis of hydrocodone compared to acetaminophen and ibuprofen for post-nail procedure analgesia
Short Title:	Hydrocodone for post-nail surgery analgesia
Clinical Phase:	Phase 4
Principal Investigator:	Shari R. Lipner MD, PhD
Study Description:	Nail surgery is associated with moderate to severe postoperative pain. The purpose of this study is to assess the efficacy and safety of ropivacaine and hydrocodone for post-nail procedure analgesia.
Sample Size:	N = 20 participants.
Enrollment:	This study will enroll 20 subjects and screen up to 30
Study Population:	Patients 18 years and older undergoing fingernail biopsies at the Weill Cornell Medicine, Department of Dermatology, specialty nail clinic.
Enrollment Period:	07/01/2022 ± 07/01/2023
Study Design:	This is a randomized, open-label study, assessing the efficacy and safety of: **group a:** intraoperative ropivacaine 0.75% + lidocaine 1% and hydrocodone 5 mg + acetaminophen 325 mg (every 4 hours for 2 days, starting 6 hours after surgery) for nail procedure-associated analgesia, compared with **group b:** intraoperative ropivacaine 0.75% + lidocaine 1% and acetaminophen 1000 mg + ibuprofen 400 mg (every 6 hours for 6 days, starting 6 hours after surgery). The Wong-Baker scale 0-to-10 scale will be used to quantitate pain scores prior to surgery, at 3 time points during surgery, and postoperatively (days 0-6). Subjects will be asked to complete a daily log where they will record pain twice daily during the postoperative period. Also, the APS-POQ-R quality of life survey will be completed on postoperative days 3 and 6. Any side effects will be recorded throughout the study period.
Description of Sites/ Facilities Enrolling Participants:	Weill Cornell Dermatology - 1305 York Avenue, NY, NY 10021
Study Duration:	1 year
Participant Duration:	6 days

Study Agent/Device Name

Intervention Description:

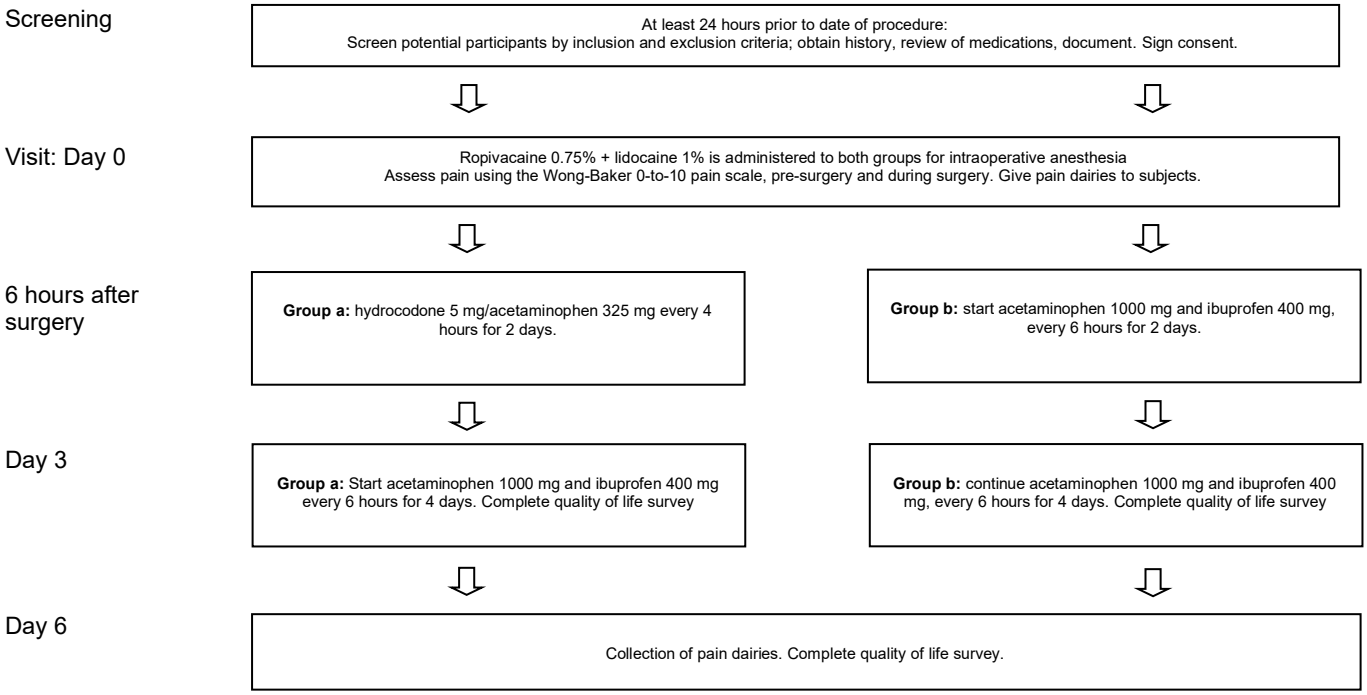
Lidocaine 1% (duration of action: 1-2 hours) and ropivacaine 0.75% (duration of action: 8 hours) are short- and long-acting local anesthetics, respectively. A mix of these will be used for intraoperative/postoperative anesthesia in both study groups. In addition, subjects in **group a** will receive: oral hydrocodone 5 mg (moderate-strength

opioid)/acetaminophen 325 mg (non-opioid analgesic), every 4 hours for 2 days, starting 6 hours after surgery. On postoperative day 3, subjects in **group a** will switch to oral acetaminophen 1000 mg and ibuprofen 400 mg every 6 hours, until postoperative day 6. Patients in **group b** will receive: acetaminophen 1000 mg and ibuprofen 400 mg, every 6 hours, for 6 days, starting 6 hours after surgery. Ropivacaine and lidocaine are FDA-approved for surgical anesthesia. Hydrocodone, acetaminophen, and ibuprofen are FDA-approved for postoperative analgesia.

Primary Objective:	The primary objective of this study is to determine the efficacy and safety of hydrocodone/acetaminophen + acetaminophen and ibuprofen vs. acetaminophen + ibuprofen, for nail procedure-associated pain management.
Secondary Objectives:	The secondary objective of this study is to determine the impact of hydrocodone/acetaminophen + acetaminophen and ibuprofen vs. acetaminophen + ibuprofen on health-related quality of life associated with pain.
Primary Endpoints:	The primary efficacy endpoint will be the change in pain scores obtained with the Wong-Baker 0-to-10 pain scale between the 2 groups on post-operative day 2.
Secondary Endpoints:	The secondary endpoint will be the change in health-related quality of life associated with pain obtained with an adapted version of the APS-POQ-R between the 2 groups on post-operative days 3 and 6.

1.1 Schema

Flow diagram



1.2 Study Objectives and End Points

1.2.1 Primary Objectives

The primary objective of this study is to determine the efficacy and safety of hydrocodone/acetaminophen + acetaminophen and ibuprofen vs. acetaminophen + ibuprofen, for nail procedure-associated pain management.

1.2.2 Secondary Objectives

The secondary objective of this study is to determine the impact of hydrocodone/acetaminophen + acetaminophen and ibuprofen vs. acetaminophen + ibuprofen on health-related quality of life associated with pain.

1.2.4 Primary Endpoints

The primary efficacy endpoint will be the change in pain scores, obtained with the Wong-Baker 0-to-10 pain scale, between the 2 groups on postoperative day 2.

1.2.5 Secondary Endpoints

The secondary endpoint will be the change in subject reported health-related quality of life associated with pain, obtained with an adapted version of the APS-POQ-R, between the 2 groups on postoperative days 3 and 6.

2. Background

2.1 Disease

Nail procedures are associated with moderate to severe postoperative pain that can be present up to one week post-op.[1] While ropivacaine has been shown to be effective for pain management after nail surgical procedures in the immediate postoperative (up to 48 hours following surgery), studies assessing safety and efficacy of pain management regimens have been limited.[2] Research on Mohs micrographic surgery have shown that the combination of oral acetaminophen 1000 mg + ibuprofen 400 mg, given every 4 hours for up to 4 doses (non-opioid analgesics) is more effective and has a lower risk of side effects than acetaminophen + codeine (opioid analgesic) and acetaminophen alone, for postoperative analgesia.[3] However, as opposed to nail surgical procedures, Mohs micrographic surgery is only associated with mild postoperative pain (2, 1.5 out of 10 on postoperative days 0-1, respectively).[4] It is currently unknown whether this combination is also superior for post-nail procedure analgesia. Effective postsurgical pain control affects patient satisfaction, reduces morbidity, and improves return to daily activities and to work.[5] It is therefore essential to determine optimal pain management alternatives for nail procedure-associated pain.

References

1. Ricardo JW, Qiu Y, Lipner SR. Longitudinal perioperative pain assessment in nail surgery. Jounral of the American Academy of Dermatology. 2021 Nov 26;S0190-9622(21)02911-X.
2. Di Chiacchio N, Ocampo-Garza J, Villarreal-Villarreal CD, Ancer-Arellano J, Noriega LF, Di Chiacchio NG. Post±nail procedure analgesia: A randomized control pilot study. Journal of the American Academy of Dermatology. 2019 Sep 1;81(3):860-2.
3. Sniezek PJ, Brodland DG, Zitelli JA. A randomized controlled trial comparing acetaminophen, acetaminophen and ibuprofen, and acetaminophen and codeine for postoperative pain relief after Mohs surgery and cutaneous reconstruction. Dermatologic surgery. 2011 Jul;37(7):1007-13.
4. Firoz BF, Goldberg LH, Arnon O, Mamelak AJ. An analysis of pain and analgesia after Mohs micrographic surgery. Journal of the American Academy of Dermatology. 2010 Jul 1;63(1):79-86.
5. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. JAMA surgery. 2017 Mar 1;152(3):292-8.

2.2 Investigational Agent/Device, or Surgical Treatment/Method

Lidocaine 1% (duration of action: 1-2 hours) and ropivacaine 0.75% (duration of action: 8 hours) are short and long-duration of action local anesthetics, respectively. A mix of these will be used in groups a and b, infiltrated with a wing block (approximately 4 injections into the nail folds and hyponychium) for intraoperative anesthesia, using a 30-gauge needle, with approximately 1 ml of solution injected in total. In addition, subjects in group a will receive:

oral hydrocodone 5 mg (moderate-strength opioid analgesic)/acetaminophen 325 mg (non-opioid analgesic), every 4 hours for 2 days (12 doses in total), starting 6 hours after surgery. On postoperative day 3, patients in group a will switch to oral acetaminophen 1000 mg + ibuprofen 400 mg every 6 hours, until day 6. Patients in group b will receive: acetaminophen 1000 mg + ibuprofen 400 mg every 6 hours, starting 6 hours after surgery, for 6 days. Ropivacaine and lidocaine are FDA-approved for surgical anesthesia. Hydrocodone/acetaminophen, acetaminophen and ibuprofen are FDA-approved for treatment of acute-pain management.

2.3 Rationale

Treatment regimens for nail procedure-associated postoperative pain are not well studied. While pain management guidelines for cutaneous procedures exist, consensus for nail surgical procedures is lacking. Randomized controlled trials are the mainstay for development of safe and effective treatments. Therefore, there is a need for randomized controlled studies objectively assessing the efficacy and safety of available analgesic regimens for management of pain associated to nail surgical procedures. We hope that the UHVXOWVRIWKHSUHVHQWVWXG\ZLOOJXLGHQDLOVXUJHRQVWRLPSURYH quality of life following nail surgery.

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

Pain associated with anesthetic infiltration, digital ischemia or necrosis. Potential side effects of opioid analgesic hydrocodone include: nausea, vomiting, constipation, somnolence, headache, euphoria and agitation. Potential severe-adverse reactions include life-threatening respiratory depression, addiction, abuse, opioid withdrawal, serotonin syndrome (when used with serotoninergic agents) and adrenal insufficiency. Hydrocodone is a controlled substance and classified as a Schedule III drug, indicating that it has medical usefulness, but also a potential for physical and psychological dependency abuse. Potential risks of acetaminophen use include skin rash, hypersensitivity reaction, nephrotoxicity, hepatotoxicity, anemia, leukopenia, neutropenia, pancytopenia and gastrointestinal reactions such as nausea, stomach pain, loss of appetite. Severe liver damage may occur if taking more than 4000 mg in 24 hours, combining with other drugs containing acetaminophen, or consuming 3 or more alcoholic beverages daily. Potential risks of ibuprofen include gastritis, ulceration, hemorrhage or perforation, nephrotoxicity, skin rash and other hypersensitive reactions.

2.4.2 Known Potential Benefits

Lidocaine 1% and ropivacaine 0.75% are FDA-approved for intraoperative anesthesia, adequately controlling pain for up to 8 hours following surgery. Hydrocodone, acetaminophen and ibuprofen are all FDA-approved for treatment of acute pain, and may provide adequate control of postoperative pain associated with nail surgical procedures.

2.4.3 Assessment of Potential Risks and Benefits

Nail surgical procedures are associated with moderate to severe pain. Although opioid and non-opioid analgesics are associated with various severe side effects, these are fortunately rare. Therefore, the benefit of the assessed interventions in the way of pain reduction may surpass the associated risks.

3. Study Design

3.1 Overall Design

This is a single center, randomized, controlled, open-label study of 20 patients undergoing fingernail or toenail biopsies. Patients will be consented at least 24 hours prior to their nail procedure. All other study procedures outside of the nail biopsy can be conducted remotely. All surgical procedures will be performed by principal investigator Dr. Shari Lipner following standardized procedure. A mix of ropivacaine 0.75% + lidocaine 1% will be used for intraoperative anesthesia for all patients. Patients will be randomized into 1 of 2 groups:

Group a: Oral hydrocodone 5 mg (moderate-strength opioid analgesic)/acetaminophen 325 mg (non-opioid analgesic), every 4 hours for 2 days (12 doses in total), starting 6 hours after surgery. On postoperative day 3, patients in group a will switch to oral acetaminophen 1000 mg + ibuprofen 400 mg every 6 hours, until day 6.

Group b: Patients in group b will receive: acetaminophen 1000 mg + ibuprofen 400 mg every 6 hours, starting 6 hours after surgery, for 6 days.

The Wong-Baker 0-to-10 pain scale will be used to quantitate pain scores in all participants prior to surgery, intraoperatively and during postoperative days 0-6 (once in the morning and evening).

An adapted version of the American Pain Society Patient Outcome Questionnaire for nail surgical pain will be used to quantitate health-related quality of life associated with pain on postoperative days 3 and 6.

Adverse Events and Reporting
Adverse events (AE) assessment will be ongoing throughout the study. All adverse events shall be reported by the clinical Investigator to the IRB as described below.

Adverse Device Effect (ADE)
Any sign, symptom, or disease in a study subject that occurs during the course of a clinical trial that is determined by the investigator to have a causal relationship or possible causal relationship with the device under investigation.

Serious Adverse Event (SAE)
Any untoward medical occurrence in a subject, regardless of whether the event is related to the device that:

a. results in death;

b. results in a life-threatening illness or injury;
c. results in a permanent impairment of a body structure or body function;
d. requires in-subject hospitalization or prolongation of existing hospitalization
e. requires a medical or surgical intervention that was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.
f. If exposed prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
g. Does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) must be reported within 24 hours of knowledge of the event to the IRB.

Unanticipated Adverse Device Effect (UADE) Any serious adverse effect on health and 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 application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

The Investigator shall be responsible for determination of the causal relationship of all adverse events to the device and/or procedure. The Principal Investigator is responsible for monitoring the safety of the subjects enrolled.

Any serious adverse events will be reviewed and analyzed by the Principal Investigator as VRRQDVWKHHYHQWRFFXUVDQGZLOOEHGRFXPHQWHGLQWKHVXEMHFW

3.2 Scientific Rationale for Study Design

This is a pilot, randomized, controlled, open-label study assessing the use of hydrocodone + acetaminophen and acetaminophen + ibuprofen vs. acetaminophen + ibuprofen alone for pain management after nail surgical procedures.

3.3 Justification for Dose

The dosage herein included has been assessed in previous studies on analgesic regimens for Mohs micrographic surgery. There are currently no guidelines on the preferred analgesic regimen for post-nail surgery analgesia.

3.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study. The end of the study is defined as completion of the last visit or procedure.

4. Subject Selection

4.1 Study Population

Subjects 18 years and older undergoing fingernail or toenail, excision or shave biopsy at specialized nail clinic, WCM Department of Dermatology for any diagnosis.

4.2 Inclusion Criteria

1. Patients undergoing fingernail or toenail, excision, or shave biopsy
2. Must understand and voluntarily sign an informed consent form
3. Must be male or female and aged 18-95 years at time of consent
4. Must be able to adhere to the study visit schedule and other protocol requirements

4.3 Exclusion Criteria

1. Subject is unable to provide written informed consent for any reason.
2. Subject has peripheral vascular disease, arterial insufficiency, peripheral neuropathy
3. Subject is on Aspirin, NSAIDs, or consumes a chronic medication for control of any other chronic pain.
4. Subject has a history of opioid or alcohol use disorder.
5. Subject has a history of peptic ulcer disease, gastritis, chronic renal insufficiency or a history of kidney disease, or has underlying liver disease
6. Subject has a history of severe constipation.
7. Subject is sensitive or allergic to any of the elements included in this study.
8. Subject is unable to complete the required pain dairy.
9. Subject is pregnant, planning pregnancy, or nursing.

4.4 Lifestyle Considerations

During this study, participants are asked to:

- Abstain from using any other analgesics different than the ones herein included as well as any other treatment modality aiming to improve pain after nail surgery.

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failures) because of a modifiable factor may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

4.6 Strategies for Recruitment and Retention

Patients attending Weil Cornell Medicine, Department of Dermatology, specialized nail clinic for fingernail or toenail biopsy. 20 participants will be offered to be included in the study and approximately 30 patients will be screened. All participants will be enrolled in:

Weill Cornell Dermatology - 1305 York Avenue, New York, NY 10021

In the present study, participants will not be compensated or provided any incentives.

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

6. Study Procedures

6.1 Schedule of Assessments

Table 1. Schedule of trial event

	Screening	Visit: Day 0	Day 3	Day 6
Informed consent	X			
Demographics	X			
Medical history	X			
Physical exam	X			
Concurrent medications	X	X	X	X
Adverse event evaluation		X	X	X
Ropivacaine + lidocaine administration		X		
Hydrocodone/acetaminophen		X	X	
Acetaminophen + ibuprofen		X	X	X
Patient quality of life survey			X	X
Efficacy assessment				X

6.1.1 Screening Visit

At the screening visit, all inclusion and exclusion criteria will be reviewed. Obtaining history and review of medications will take place.

6.1.2 Treatment Phase

Subjects who fulfill all inclusion and exclusion criteria, and sign informed consent are eligible to enroll and begin baseline visit procedures 24 hours after signing consent. After this baseline visit, all other procedures can be conducted remotely, including collection of pain diaries, medication history, and quality of life survey.

Nail biopsy will be performed under standardized procedure by principal investigator Dr. Shari Lipner. A mix of ropivacaine 0.75% + lidocaine 1% will be infiltrated for intraoperative anesthesia.

6 hours after nail surgery:

Patients in **group a:** start oral hydrocodone 5 mg (moderate-strength opioid analgesic)/acetaminophen 325 mg (non-opioid analgesic), every 4 hours for 2 days (12 doses in total)

Patients in **group b:** start acetaminophen 1000 mg + ibuprofen 400 mg every 6 hours for 2 days.

On postoperative day 3:

Patients in **group a:** switch to oral acetaminophen 1000 mg + ibuprofen 400 mg every 6 hours, until postoperative day 6.

Patients in **Group b:** continue acetaminophen 1000 mg + ibuprofen 400 mg every 6 hours, until postoperative day 6.

7. Study Intervention

7.1 Study Intervention/Device Description

Lidocaine 1% (duration of action: 1-2 hours) and ropivacaine 0.75% (duration of action: 8 hours) are short- and long-acting local anesthetics, respectively. A mix of these will be used for intraoperative/postoperative anesthesia in both study groups. In addition: subjects in **group a** will receive: oral hydrocodone 5 mg (moderate-strength opioid)/acetaminophen 325 mg (non-opioid analgesic), every 4 hours for 2 days, starting 6 hours after surgery. On postoperative day 3, subjects in **group a** will switch to oral acetaminophen 1000 mg and ibuprofen 400 mg every 6 hours, until postoperative day 6. Patients in **group b** will receive: acetaminophen 1000 mg and ibuprofen 400 mg, every 6 hours, for 6 days, starting 6 hours after surgery. Ropivacaine and lidocaine are FDA-approved for surgical anesthesia. Hydrocodone, acetaminophen, and ibuprofen are FDA-approved for postoperative analgesia.

7.2 Availability

Ropivacaine 0.75%, lidocaine 1%, hydrocodone 5 mg/acetaminophen 325 mg, acetaminophen 500 mg and ibuprofen 200 mg are widely available in pharmacies, and will be purchased by WCM Medicine, Department of Dermatology, for the purpose of this study.

7.3 Acquisition and Accountability

Inventory Records/Device Logs ± The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and all medications here included.

7.4 Formulation, Appearance, Packaging, and Labeling

Ropivacaine hydrochloride injection 0.75% (150 mg/20 ml) glass vial
Lidocaine hydrochloride injection 1% (300 mg/30 ml) glass vial
Hydrocodone bitartrate and acetaminophen tablets 5 mg/325 mg (12 tablets will be prescribed; Vicodin)
Acetaminophen 500 mg each tablet (Tylenol Extra Strength)
Ibuprofen 200 mg each tablet (Advil)

7.5 Product Storage and Stability

All medications herein included will be stored in a dry place with temperature 60°F ± 90°F

7.6 Preparation

A mix of 0.5 ml ropivacaine 0.75% and 0.5 ml lidocaine 1% will be used for intraoperative/postoperative anesthesia.

7.7 Dosing and Administration

Approximately 0.5 ± 1 ml of anesthetic mix will be infiltrated for intraoperative/postoperative anesthesia with a wing digital block. Dosage of all other medications will be:

- Oral hydrocodone 5 mg (moderate-strength opioid)/acetaminophen 325 mg (non-opioid analgesic), every 4 hours for 2 days, starting 6 hours after surgery.
- Acetaminophen 1000 mg and ibuprofen 400 mg every 6 hours, for 4 or 6 days (depending on the group)

7.7.1 Dosing Delays/Dose Modifications

Not applicable.

7.8 General Concomitant Medication and Supportive Care Guidelines

All concomitant medications will be recorded and/or updated on subject medication chart throughout the course of the study and saved in subject binder, if applicable.

7.9 Duration of Therapy and Criteria for Removal from Study

In the absence of treatment delays due to adverse event(s), oral hydrocodone 5 mg (moderate-strength opioid)/acetaminophen 325 mg (non-opioid analgesic) will be consumed

for a maximum of 2 days (every 4 hours, 12 doses in total). Acetaminophen 1000 mg and ibuprofen 400 mg will be consumed for up to 6 days (every 6 hours), depending on the group.

The treatment may will be discontinued prior to the time specified above in the case of below events:

- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Subject decides to withdraw from the study, or
- General or specific changes in the subject¶VFRQGLWLRQ\HQGHUWKH unacceptable for further treatment in the judgment of the investigator.

Study Termination Guidelines: $VXEMHFW¶V-uprRtocol study will end after one of the following applies:

- 6XEMHFW¶VYROXQWDU\ZLWKGUDZDO •
  Subject lost to follow-up
- Subject death
- Completion of all scheduled study follow-up appointments
- Any other rules specific to your study

7.10 Duration of Follow Up

Subjects will be followed for 3 days after their last dose. Subjects removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.11 Measures to Minimize Bias: Randomization and Blinding

This is a pilot open label study. A randomization table will determine subject allocation to each group (10 subjects in **group a** and 10 subjects in **group b**).

7.12 Study Intervention/Follow-up Compliance

During the baseline visit (standard of care visit), participants will be asked to provide their best way of contact. All other study procedures will be conducted remotely. There are no more in-person visits required for this study.

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

Participants may withdraw voluntarily from the study or the PI may discontinue a participant from the study. Participants will be excluded if they have/develop peripheral neuropathy or any other condition precluding the accurate measurement of pain. The subject gets pregnant, is planning pregnancy, or is nursing. The subject has/develops peripheral vascular disease or arterial insufficiency.

8.1 Discontinuation of Study Intervention

Discontinuation from treatment regimens means discontinuation from the study. However, if a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason(s) for discontinuation, take digital photographs, assessment of concomitant medications.

8.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study intervention(s)
- Participant lost to follow-up after several attempts to contact subject to schedule study visit.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

8.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she fails to return for one or more scheduled visits and is unable to be contacted by the study site staff.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit up to 7 days after the 4 weeks from the previous visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and if possible, 1 email). These contact attempts should be GRFXPHQWHGLQWKHSDUWLFLSDQW¶VPHGLFDOUHFRUGRUVWXG\IL

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Correlative/Special Studies

Not applicable

10. Measurement of Effect

Pain levels will be measured using the Wong-Baker FACES 0-to-10 pain scale:

Health-related quality of life associated with pain will be measured using an adapted version of the American Pain Society Patient Outcome Questionnaire:

1. **On this scale, please indicate the least pain you had today.**

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10
no pain worst pain possible

2. **On this scale, please indicate the worst pain you had today.**

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10
no pain worst pain possible

3. **On this scale, please indicate the average pain you had today.**

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10
no pain worst pain possible

4. **How often were you in severe pain in the first 24 hours? Please mark your best estimate of the percentage of time you experienced severe pain.**

○ 0% ○ 10% ○ 20% ○ 30% ○ 40% ○ 50% ○ 60% ○ 70% ○ 80% ○ 90% ○ 100%
Never in severe pain Always in severe pain

5. **Mark the one number below that best describes how much pain interfered or prevented you from:**

a. **Moving around**

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10
Does not interfere Completely interferes

b. **Doing daily activities of living**

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10
Does not interfere Completely interferes

c. **Falling asleep**

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10
Does not interfere Completely interferes

d. **Staying asleep**

○ 0 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10
Does not interfere Completely interferes

6. **Pain can affect our mood and emotions. On this scale, please circle the one number that best shows how much the pain caused you to feel:**

a. Anxious	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6	○ 7	○ 8	○ 9	○ 10
	Not at all										Extremely
b. Depressed	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6	○ 7	○ 8	○ 9	○ 10
	Not at all										Extremely
c. Frightened	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6	○ 7	○ 8	○ 9	○ 10
	Not at all										Extremely
d. Helpless	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6	○ 7	○ 8	○ 9	○ 10
	Not at all										Extremely

10.1 Response Criteria

Change in the pain level from baseline to postoperative days 2 and 6.

10.2 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

10.3 Progression-Free Survival

Not Applicable.

10.4 Other Response Parameters

Please see section **12.5 Secondary Endpoints.**

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group-based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF,

or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-*&3DQGORFDOUHJXODWLRQVDVDSSOLFDEOHIURPHDFKSRWHQWLDO legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws and regulations.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the

Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

12.1 Study Design/Endpoints

For study design, please see section **3. Study Design.**

Endpoints

The Primary efficacy endpoint will be the change in pain scores obtained with the Wong-Baker 0-to-10 pain scale between the 2 groups.

The secondary endpoint will be the change in health-related quality of life associated with pain between the 2 groups.

12.2 Sample Size/Accrual Rate

20 patients undergoing fingernail or toenail, excision or shave biopsy will be included.

12.3 Stratification Factors

Not applicable.

12.4 Analysis of Endpoints

12.4.1 Analysis of Primary Endpoints

Please see **section 12.1 Study design/Endpoints**

12.4.2 Analysis of Secondary Endpoints

Please see **section 12.1 Study design/Endpoints**

12.5 Interim Analysis

Not applicable.

12.6 Reporting and Exclusions

12.6.1 Evaluation of Toxicity

All subjects will be evaluable for toxicity from the time of anesthesia infiltration, until follow-up is completed (3 days after postoperative day 6).

12.6.2 Evaluation of Response

All subjects included in the study will be assessed for response to treatment if they have received one treatment.

13. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

13.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

13.1.1 Investigational Agent or Device Risks (Expected Adverse Events)

Pain associated with anesthetic infiltration, digit ischemia or necrosis. Potential side effects of opioid analgesic hydrocodone include: nausea, vomiting, constipation, somnolence, headache, euphoria and agitation. Potential severe-adverse reactions include life-threatening respiratory depression, addiction, abuse, opioid withdrawal, serotonin syndrome (when used with serotoninergic agents) and adrenal insufficiency. Hydrocodone is a controlled substance and classified as a Schedule III drug, indicating that it has medical usefulness, but also a potential for physical and psychological dependency abuse. Potential risks of acetaminophen use include skin rash, hypersensitivity reaction, nephrotoxicity, hepatotoxicity, anemia, leukopenia, neutropenia, pancytopenia and gastrointestinal reactions such as nausea, stomach pain, loss of appetite. Severe liver damage may occur if taking more than 4000 mg in 24 hours, combining with other drugs containing acetaminophen, or consuming 3 or more alcoholic beverages daily. Potential risks of ibuprofen include gastritis, ulceration,

hemorrhage or perforation, nephrotoxicity, skin rash and other hypersensitive reactions.

13.1.2 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite ± The AE *is clearly related* to the study treatment.
  - Probable ± The AE *is likely related* to the study treatment. ○ Possible ± The AE *may be related* to the study treatment.
  - Unlikely ± The AE *is doubtfully related* to the study treatment.
  - Unrelated ± The AE *is clearly NOT related* to the study treatment.

13.1.3 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject¶VUHVHDUFKFKDUW

13.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.1.5 Reporting Events to Participants

Not applicable.

13.1.6 Events of Special Interest

Not applicable

13.1.7 Reporting of Pregnancy

Discontinuation of study intervention, while continuing safety follow-up, requesting permission to follow pregnant women to pregnancy outcome.

13.2 Definition of SAE

SAEs include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.2.2 Reporting of SAE to FDA [For Protocols Where WCMC is the Sponsor-Investigator]

IND application sponsor must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected. Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than 7 FDOHQGDUGD\VIROORZLQJWKHVSRQVRU¶VLQLWLDOUHFHLSWRIWKHLQ i. death,

ii. a life-threatening adverse event,
iii. in-patient hospitalization or prolongation of existing hospitalization,
iv. a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
v. a congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or research subject and may require medical or surgical intervention to prevent one of the outcomes listed as serious

CDER-only Biologic INDs:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biologic Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

13.2.3 Reporting of SAE to KeryFlex, Pod-Advance, Inc

Institution will send KeryFlex, Pod-Advance, Inc copies of any and all serious adverse event reports filed with the FDA or other applicable regulatory authorities, as well as copies of any correspondence with the FDA or other applicable regulatory authorities, regarding any and all serious adverse events, irrespective of association with the Study Drug(s) in the course of the Clinical Trial, within 30 business days of such report or correspondence being sent to the FDA or other applicable regulatory authorities. Copies should be faxed directly to Eclipse Medical at (866)-558-0415.

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject

discontinues participation from the study.

13.4 Time Period and Frequency for Event Assessment and Follow Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes HYHQWGHVFULSWLRQWLPHRIRQVHWFOLQLFLDQ¶VDVVHVVPHQWRIVHYHU product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered DVEDVHOLQHDQGQRWUHSRUWHGDVDQ$(+RZHYHULIWKH condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Jonathan Hwang or Jose Ricardo will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

14. Unanticipated Problems Involving Risks to Subjects or Others

14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

This definition could include an unanticipated adverse device effect, 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 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 (21 CFR 812.3(s)).

14.1.2 Unanticipated Problem Reporting

An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)), A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the

results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1)).

15. Data and Safety Monitoring Plan (DSMP)

In this section, please include a written plan of the measures that will be taken to ensure the safety of clinical research subjects and protect the validity and integrity of research data. The following questions should be addressed as a part of the DSMP and must be incorporated into your WCM eIRB application:

- Include a description of the proposed monitoring entity (i.e. WCM DSMB, Independent Medical Monitor) and rationale for choosing the specified monitoring entity. If you are using an independent medical monitor or study monitoring committee/group, please specify their qualifications.
- Describe the data/events that will be captured and submitted to the monitoring entity. Specify what data will be collected during the course of the study to assess both safety and efficacy.
- Describe what adverse events may cause the subject to terminate protocol treatment. Specifically, describe treatment stopping rules for an individual subject.
- How will adverse events and unanticipated problems be reported to the monitoring entity and with what frequency?
- How often will the monitoring entity review data/events (i.e. annually, semi-annually, etc.)
- Describe the complete study stopping rules (criteria for study suspension and potential study termination) statistical considerations. If there are no defined stopping rules, please provide a rationale. Also, state any specific triggers for action.
- All dose escalation trials are required to define dose limiting toxicities, rules for escalation of dose, and criteria for stopping the trial and defining the Maximum Tolerated Dose.
- How will the monitoring HQWLW\¶VFRPPHQWVUHYLHZEHGLVVHPLQDWHG"HJ the IRB at the time of continuing review and submitted to participating sites upon receipt of review comments.)