CLINICAL STUDY PROTOCOL

Compound Name:	N1539 (meloxicam) Injection, for intravenous use
Protocol Number:	BDX-20-002
Protocol Title:	A Phase 4, Multicenter, Open-Label Study to Evaluate the Safety and Pharmacokinetics of N1539 in Children 2 to <17 Years of Age Following Surgery
Date of Protocol:	23 August 2021
Study Designated Physician:	Stewart McCallum, MD 490 Lapp Rd Malvern, PA 19355 Mobile: Fax: Email:
Contact:	Alex Freyer Clinical Scientist 490 Lapp Rd Malvern, PA 19355 Mobile: Email:

INVESTIGATOR'S AGREEMENT

By signing below, I confirm that I have read this protocol (BDX-20-002) and agree:

- to assume responsibility for the proper conduct of the study at this site
- to conduct the study according to the procedures described in this protocol and any future amendments
- not to implement any deviation from, or changes to, the protocol without agreement of the sponsor and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to eliminate an immediate hazard to subject(s)
- that I am aware of and will comply with all applicable regulations and guidelines

Principal Investigator's Signature	**Date**

Principal Investigator's Name (Print)

Principal Investigator's title (Print)

Site Address:

PROTOCOL SYNOPSIS

Name of Sponsor/Company: Baudax Bio, Inc.	**Protocol Number:** BDX-20-002
Name of Study Drug: N1539 (meloxicam) Injection, for intravenous use	**Protocol Title:** A Phase 4, Multicenter, Open-Label Study to Evaluate the Safety and Pharmacokinetics of N1539 in Children 2 to <17 Years of Age Following Surgery
Name of Active Ingredient: meloxicam	**Phase of Development:** 4

Objectives: The objectives of this study are:

- To determine the safety and tolerability of N1539 in children 2 to <17 years of age
- To characterize the pharmacokinetics (PK) of N1539 in children 2 to <17 years of age

Methodology: This is an open-label, multicenter study in children 2 to <17 years of age, who are scheduled for elective surgery in an inpatient or outpatient setting. Eligible subjects will be enrolled in three groups according to age (i.e., 12 to <17 years, 7 to <12 years, 2 to <7 years). Enrollment will start with the oldest age group (12 to <17 years) and will continue in a descending step-wise fashion until the safety and PK of N1539 is established for all three age groups. All enrolled subjects will be included in the safety assessment and analyses, while PK will be assessed in a subset of each age group (N=12 per age group).

Each subject will be screened for eligibility within 28 days before undergoing elective surgery on Day 1. Eligible subjects will undergo their surgical procedure with appropriate anesthesia according to the investigator's clinical practice and in accordance with institutional standards.

At the end of the surgical procedure (Hour 0, defined as the time of last suture, staple, or steri-strip placement) each subject will receive their first dose of N1539 as an IV bolus injection according to age category as shown in the table below. Additional doses of N1539 may be administered every 24 hours (±1 hour) until the subject is either discharged from the hospital or until IV study drug analgesia is no longer clinically indicated. Subjects may receive up to a maximum of three doses of N1539.

N1539 Dosing in Children 2 to <17 Years

Age Group	Number of Subjects	N1539 Dose
Group 1: 12 to <17 years	N=30	0.6 mg/kg (not to exceed 30 mg) Q24H
Group 2: 7 to <12 years	N=30	
Group 3: 2 to <7 years	N=30	

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Subjects will receive non-NSAID standard of care analgesia according to the standard practice of the institution based upon the procedure type (Section 5.13). Other standard of care practices associated with the surgical procedure, which are not specially defined in the protocol, will be carried out according to the investigator's clinical practice and in accordance with institutional standards.

Subjects will be discharged from the study unit when deemed appropriate by the investigator based on clinical status. Subjects who are discharged from the study unit on the same day as surgery will return to the study unit the next day (Day 2) in sufficient time to allow for collection of the Hour 24 PK sample.

Subjects will have a follow-up visit at the clinical site 7 days after the last dose of study drug (LSD+7) and will be assessed primarily for adverse events (AEs) and wound healing. A final telephone interview will be conducted with the subject's parent or legal guardian 28 days after the last dose of study drug (LSD+28) to assess for AEs. After this follow-up telephone interview is completed, subjects are considered to have completed the study.

Inclusion criteria: To be eligible for inclusion into this study, subjects must:

1. Be a male or female 2 to <17 years of age before dosing on Day 1.
2. Be eligible for elective surgery that will be performed according to standard surgical technique under appropriate anesthesia.
3. Be premenarche or have confirmed negative urine pregnancy testing before surgery on Day 1, if an adolescent female of childbearing potential.
4. Be willing and able to cooperate with all the requirements of the study.
5. Be able to speak and understand English or Spanish.
6. Have a legally authorized representative (e.g., parent, guardian) who is able to read, speak, and understand English or Spanish and who will voluntarily sign and date a parental permission/informed consent form that is approved by the Institutional Review Board/Independent Ethics Committee/Human Research Ethics Committee (IRB/IEC/HREC).
7. Be willing to sign an assent (if appropriate dependent upon the subject's age, understanding, and IRB requirements), before the conduct of any study procedure.

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Exclusion Criteria: A subject will be excluded from study participation if prior to the surgical procedure he/she:

1. Has a known allergy or hypersensitivity to meloxicam, aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), or any excipient of N1539.
2. Has a known bleeding disorder that may be worsened with the administration of an NSAID.
3. Is undergoing cardiothoracic surgery.
4. Has used meloxicam within 7 days before the surgical procedure on Day 1.
5. Is currently taking any medication, food, beverage, or herbal supplement that interferes with CYP3A4 or CYP2C9 metabolism and is unable to discontinue this medication, food, beverage, or herbal supplement at least 14 days before administration of N1539 on Day 1 and continuing through collection of the final PK sample on Day 2 (24 hours after administration of N1539).
6. Is unable to discontinue any medication (prescription or over-the-counter [OTC]) within 5 half-lives of the specific medication (or within 48 hours if the half-life is unknown) before administration of N1539 on Day 1. The only exceptions are oral contraceptives, acetaminophen, and those medications utilized during the preparation of the subject for surgery.
7. Has evidence of a clinically significant 12-lead electrocardiogram (ECG) abnormality as determined by the investigator.
8. Has participated in a clinical trial (investigational or marketed product) within 30 days before surgery.
9. Has any clinically significant medical history or clinical manifestations of significant cardiac, neurological, immunological, renal, hepatic, or hematological disease or any other condition that in the opinion of the investigator, substantially increases the risk associated with the subject's participation in the study or compromises the scientific objectives of the study.

Safety Assessments: Safety will be assessed during the study through the recording of adverse events, vital signs, electrocardiograms, and the evaluation of wound healing.

Pharmacokinetic Assessments: Whole blood samples (1.5 mL) for pharmacokinetic assessment will be collected in subjects assigned to the PK group at each of the following time points: any time before the first dose of N1539 on Day 1 and 5 minutes and 1, 3, and 24 hours (to be collected prior to Dose 2) after Dose 1. A total of approximately 7.5 mL of whole blood will be collected from each subject assigned to the PK group for PK analyses.

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Sample Size: Based on modeling and simulations, a study design with 12 subjects per age group and five PK samples (i.e., pre-dose, 5 minutes and 1, 3, 24 hours after the initial dose) is expected to provide a robust estimation of clearance (CL) and volume of distribution (V) in pediatric subjects in each age group (RECR-CSC-103). This study design has a statistical power >80% for obtaining 95% confidence intervals for CL and V within the pre-defined 60% to 140% acceptance range (Wang 2012, FDA guidance UCM425885), which should enable accurate assessment of PK parameters following administration of meloxicam IV to pediatric subjects.

Study populations:

Intent-to-Treat (ITT) Population: The ITT population will include all subjects who are enrolled in the study, defined as informed consent signed by the parent or legal guardian and assent obtained from the child (as appropriate) and all eligibility criteria met. ITT subjects may or may not receive N1539.

Safety Population: The safety population will include of all subjects who receive at least one dose of N1539. All safety evaluations will be based on the safety population.

Pharmacokinetic Population: The PK population will include all subjects who receive N1539 and have at least one PK sample above the lower level of quantification (LLQ) for the determination of plasma meloxicam levels.

Safety: Safety endpoints include incidence of AEs and serious adverse events (SAEs), incidence of clinically significant changes in vital signs, incidence of clinically significant abnormal ECG findings, and investigator assessment of wound healing.

Summary statistics will be prepared for all measured safety endpoints by dose group and study overall.

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Pharmacokinetics: Pharmacokinetic endpoints for the determination of meloxicam concentrations in plasma will be based on a population PK analysis in pediatric subjects who have at least one PK sample above the LLQ. Relevant covariates (i.e., body weight and estimated glomerular filtration rate) will also be integrated into the population PK analysis.

Individual parameters of N1539 in pediatric subjects will be obtained by fitting the models to the PK data. Primary PK endpoints (i.e., CL and V) will be generated with other parameters (i.e., terminal elimination half-life [$t_{1/2}$], and steady-state volume of distribution [Vss]).

The following exposure parameters will also be derived based on simulated rich concentration-time profiles using the actual dosing history and individual PK parameters: area under the curve from time zero to time infinity ($AUC_{0-\infty}$), maximum concentration (C_{max}) and minimum concentration (C_{min}).

Individual concentrations will be summarized with descriptive statistics for each nominal time (i.e., predose, 5 min, 1, 3 and 24 hours after Dose 1) by dose group. Descriptive statistics of key parameters for N1539 (mean, standard deviation, coefficient of variation, standard error of the mean, sample size, minimum, maximum, and median) will be calculated for each age group. In addition, geometric mean and geometric coefficient of variation will be derived.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AAP	American Academy of Pediatrics
AE	Adverse event
AUC	Area under the curve
AUC_{0-24}	Area under the curve from time 0 to time 24 hours
$AUC_{0-\infty}$	Area under the curve from time 0 to time infinity
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence interval
eCRF	Electronic case report form
CL	Clearance
C_{max}	Maximum drug plasma concentration
C_{min}	Minimum drug plasma concentration
CRO	Clinical research organization
ECG	Electrocardiogram
EGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
GCP	Good clinical practice
Hour 0	Time of last suture, staple, or steri-strip placement
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonisation
IEC	Human Research Ethics Committee
IND	Investigational new drug
IRB	Institutional review board
ITT	Intent-to-treat
IV	Intravenous
LLQ	Lower level of quantification
LSD	Last study dose
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Nonsteroidal anti-inflammatory drugs
PACU	Post anesthesia care unit
PK	Pharmacokinetic
PO	Per os, by mouth
Qualified designee	Qualified by education and training to perform the study procedure (eg, subinvestigator, nurse).
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class

Abbreviation	Definition
TEAE	Treatment-emergent adverse events
$t_{1/2}$	Terminal elimination half-life
T_{max}	Time to maximum plasma concentration
US	United States
V	Volume of distribution
Vss	Steady-state volume of distribution

1. INTRODUCTION

1.1. Postsurgical Pain in Children

Pain is among the most common conditions requiring treatment in the United States (US), and is prevalent across the spectrum of subject age groups. The treatment of pain is often complex, requiring a multi-modal treatment approach. Even more complex is the treatment of pain in pediatric subjects, where misconceptions of pain can be compounded by a subject population that presents at different developmental levels.

Many physicians and some members of the medical community have previously assumed that children do not feel pain or do not remember the experiences associated with pain. It has now been established that the nervous system is sufficiently developed prior to birth to process nociception, and that treatment of pain is appropriate and necessary from the time of birth (Andrews 1999).

The greatest advance in pediatric pain medicine is the recognition that untreated pain is a significant cause of morbidity and even mortality after surgical trauma. Accurate assessment of pain in different age groups and the effective treatment of postoperative pain is constantly being refined; with newer drugs being used alone or in combination with other drugs (Verghese 2010). Several advances in developmental neurobiology and pharmacology, knowledge of new analgesics, and newer applications of old analgesics in the last two decades have helped the pediatric anesthesiologist in managing pain in children more efficiently (Verghese 2010).

Pain, particularly acute pain, in the pediatric population may occur because of injury, illness, or medical/surgical procedures. Surgical procedures, in adult and pediatric subjects, often have varying, but relatively predictable degrees of postoperative pain. With over 200,000 surgical procedures performed annually, the treatment of acute pain has a significant impact on pediatric subjects (Somme 2013).

Treatment modalities for acute pain in pediatric subjects are generally similar to those of adult subjects. Systemic opioids, NSAIDs, and regional analgesics alone or combined with additives are currently used to treat acute pain in postoperative pediatric subjects (Tamura 2013). Opioid analgesia has traditionally been used as pain control because it targets central mechanisms involved in the perception of pain (Tamura 2013; Misiolek 2014). However, since 1969, codeine has been linked to 64 cases of serious breathing problems, including 24 deaths in children and adolescents. Tramadol, although not approved for pediatric use, has been tied to nine cases of serious breathing problems, including three deaths in children and adolescents, according to the Food and Drug Administration (FDA). In September 2016, the American Academy of Pediatrics (AAP) released a clinical report that expressed concerns about the dangers of codeine use in children and called for more formal restrictions. In April 2017, the FDA issued a statement that codeine and tramadol should not be used to treat pain or cough in children younger than 12 years as they could be fatal. The FDA unveiled several changes to the labels of the medications to protect children, adolescents, and infants being breastfed (http://www.aappublications.org/news/2017/04/20/Codeine042017).

Thus, a safe and effective method to provide adequate pain relief is an extremely important aspect in the management of postsurgical pain in children. A multimodal approach that

recognizes the pathophysiology of surgical pain using several agents to decrease pain receptor activity and to diminish the local hormonal response to injury should lessen the dependence on a single medication and mechanism of action (Lovich-Sapola 2015).

1.2. Meloxicam

Meloxicam, an NSAID of the enolic acid class, was first approved for oral use in the US in 2000 and has a well-established safety profile in commercial use as an effective treatment for relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis and the relief of the signs and symptoms of pauciarticular or polyarticular course juvenile rheumatoid arthritis in children ≥60 kg (Mobic® 2016).

Meloxicam 7.5 mg once daily has been demonstrated to be safe and effective in pediatric subjects following oral administration, in the treatment of pauciarticular or polyarticular course juvenile rheumatoid arthritis. Safety observations following administration of oral meloxicam to children were reported to be generally consistent with findings in the adult populations (including rheumatoid arthritis and osteoarthritis).

Meloxicam administered orally has a slow onset of action, largely due to poor water solubility, and is not currently approved for the treatment of acute pain. It has a prolonged absorption, with the time of maximum observed plasma concentration (T_{max}) approximately 5-6 hours following oral administration (Degner 1997; Turck 1997a), which is consistent with its poor aqueous solubility. By increasing the dissolution rate of the active meloxicam moiety using Baudax Bio's proprietary NanoCrystal technology, meloxicam administered as an IV bolus injection has been shown to have a rapid onset of action (as early as 10 minutes) in adults who participated in the N1539 clinical program.

1.3. N1539 (Meloxicam) Injection, for Intravenous Use

A total of 2075 adult subjects were evaluated in 11 clinical studies; 109 subjects were healthy volunteers who received N1539 at doses ranging from 15 mg to 180 mg, placebo, or an active control in the four Phase 1 studies, and 1966 were postoperative subjects who received N1539 at doses ranging from 5 mg to 60 mg, placebo, or an active control in seven adequate and well-controlled Phase 2/3 efficacy and safety studies. Of the 1966 postoperative subjects, 1426 received at least one dose of N1539.

The following sections highlight the PK and safety of N1539 in adults. For a detailed discussion of PK, safety, and efficacy please refer to the N1539 Investigational Brochure.

1.3.1. N1539 Pharmacokinetics

Meloxicam exposure was consistently greater after IV administration of N1539 compared to oral administration of Mobic at equivalent doses. The C_{max} and AUC for N1539 were similar across the Phase 1 studies, although some variability in exposure was noted in studies with smaller sample sizes. As expected, IV administration of N1539 resulted in substantially higher C_{max} and earlier T_{max} compared with oral administration of Mobic at equivalent doses over a range of 15 to 60 mg. Eight to 12 hours after administration of equivalent doses of IV and oral meloxicam, plasma concentration-time curves were similar.

Ad hoc analyses from the Phase 1 studies demonstrated that a single dose of N1539 30 mg administered IV resulted in a slightly more than 2-fold higher AUC_{∞} and 4.65-fold higher C_{max} relative to a single dose of Mobic 15 mg administered orally (Table 1). Importantly meloxicam plasma concentrations were sustained for 24 hours after N1539 IV administration making N1539 suitable for once a day dosing. Peak and overall meloxicam exposure increased in a dose-proportional manner after administration of N1539 at doses of 15 mg, 30 mg, and 60 mg (RECR-PCS-101).

After seven consecutive 30 mg daily doses of N1539, steady state was achieved and accumulation was observed, with a roughly 2-fold increase in AUC_{∞} (Table 2). Population PK estimates of N1539 exposure were generally consistent with observed values in clinical studies.

The T_{max} for N1539 occurred almost immediately after IV administration in all Phase 1 studies, whereas absorption after oral administration of Mobic was prolonged (≈ 5 to 7 hours) and similar to that reported in the Mobic USPI (Mobic 2016).

Table 1: Single-Dose Pharmacokinetics of N1539 Injection and Oral Meloxicam

	N1539 Injection 30 mg	**Oral Meloxicam 15 mg**
Parameter		
C_{max} (ng/mL)	5642.9 ± 1009.0	1221.9 ± 289.5
T_{max} (h)	0.12 ± 0.04	6.57 ± 4.12
AUC_{inf} (ng*hr/mL)	107508.7 ± 34443.0	53988.8 ± 23207.7
$T_{½}$ (h)	23.3 ± 9.36	26.4 ± 12.1

Table 2: Single vs. Multiple-Dose Pharmacokinetics of N1539 Injection

	N1539 Injection 30 mg Single Dose	**N1539 Injection 30 mg Repeat Dose**
Parameter		
C_{max} (ng/mL)	7972.5 ± 2579.9	10632.5 ± 4729.8
AUC_{inf} (ng·hr/mL)	121437.6 ± 64505.6	297771.6 ± 241604.01
$T_{½}$ (h)	23.6 ± 10.1	26.4 ± 10.1

1.3.2. N1539 Safety

1.3.2.1. Adverse Events

During clinical development, 1426 subjects were exposed to N1539 at doses ranging from 5 mg to 60 mg in controlled and open-label Phase 2 and Phase 3 trials. In these trials, 381 subjects received a single dose of N1539 and 1045 subjects received multiple doses daily for up to 7 days. The incidence rates of adverse reactions listed in Table 3 are derived from the three Phase 3 trials comparing N1539 30 mg to placebo in subjects who may have also received narcotic rescue medication.

Table 3: Common Adverse Reactions Occurring in ≥3% of Subjects Treated With N1539 30 mg in Placebo-Controlled Phase 3 Clinical Trials

MedDRA Preferred Term	Placebo N=393	N1539 Injection 30 mg N=748
Any Adverse Reaction	253 (64.4%)	441 (59.0%)
Nausea	118 (30.0%)	173 (23.1%)
Headache	42 (10.7%)	41 (5.5%)
Constipation	24 (6.1%)	57 (7.6%)
Vomiting	33 (8.4%)	35 (4.7%)
Pruritus	15 (3.8%)	29 (3.9%)

There were no deaths among subjects who received N1539. Fifteen subjects (2.9%) in the placebo group and 20 subjects (1.4%) in the N1539 group had SAEs. All SAEs in the meloxicam group were considered unrelated to study drug. The percentage of subjects who discontinued study drug and/or the study due to an AE was low and similar between the N1539 30 mg group (0.2%) and the placebo group (0.6%). The incidence of reported AEs did not increase as the dose of N1539 increased from 5 mg to 60 mg (ISS, Module 5.3.5.3).

1.3.2.2. Clinical Laboratory Findings

There were no notable differences between the N1539 30 mg and placebo treatment groups in the percentage of subjects with potentially clinically significant hematology, chemistry, or coagulation laboratory parameters with the exception of hemoglobin, hematocrit, and albumin. A higher percentage of subjects in the N1539 30 mg group had hemoglobin and hematocrit values that shifted from normal at baseline to low during the study compared to subjects in the placebo group (hemoglobin: 36.1% versus 28.3%; hematocrit: 39.1% versus 32.4%). At the end of study visit (approximately 7 days after the last dose), hematocrit and hemoglobin trended toward baseline in the N1539 group but did not reach baseline.

A higher percentage of subjects in the N1539 30 mg group had albumin values that shifted from normal at baseline to low during the study compared to subjects in the placebo group (12.9% versus 4.4%). By the end of study visit, albumin approximated baseline in both groups. The combination of the physiologic stress of surgery in addition to NSAID induced changes in

intestinal mucosal permeability most likely contributed to the increased rate of lower albumin values in the N1539 30 mg group.

1.3.2.3. Vital Sign Findings

There were no notable differences between the N1539 30 mg and placebo treatment groups in the percentage of subjects with potentially clinically significant changes in systolic and diastolic blood pressure. The incidence of clinically significant vital sign parameters that were reported as AEs was low and generally similar between treatment groups in the pooled Phase 3 studies.

1.3.2.4. Electrocardiogram Findings

While administered as a single dose, N1539 exposures of 120 mg and 180 mg demonstrated a meaningful exposure multiple (>6 fold) compared to the 30 mg clinical dose, while maintaining a tolerability profile comparable to placebo. Results showed that therapeutic and supratherapeutic doses of N1539 up to 180 mg did not affect cardiac repolarization in the form of prolonged QTcF interval, or in other measures including heart rate, and PR and QRS intervals.

1.3.2.5. Wound Healing

Overall there was a low incidence of investigator determined clinically significant wound healing findings, and the incidence was similar between N1539 30 mg (2.1%) and placebo (2.3%).

2. STUDY OBJECTIVES

The objectives of this study are:

- To determine the safety and tolerability of N1539 in children 2 to <17 years of age
- To characterize the pharmacokinetics (PK) of N1539 in children 2 to <17 years of age

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan Description

This is an open-label, multicenter study in children 2 to <17 years of age, who are scheduled for elective surgery in an inpatient or outpatient setting. Eligible subjects will be enrolled in three groups according to age (i.e., 12 to <17 years, 7 to <12 years, 2 to <7 years). Enrollment will start with the oldest age group (12 to <17 years) and will continue in a descending step-wise fashion until the safety and PK of N1539 is established for all three age groups. All enrolled subjects will be included in the safety assessment and analyses, while PK will be assessed in a subset of each age group (N=12 per age group).

Each subject will be screened for eligibility within 28 days before undergoing elective surgery on Day 1. Eligible subjects will undergo their surgical procedure with appropriate anesthesia according to the investigator's clinical practice and in accordance with institutional standards.

At the end of the surgical procedure (Hour 0, defined as the time of last suture, staple, or steri strip placement) each subject will receive their first dose of N1539 as an IV bolus injection according to age category as shown in Table 4. Additional doses of N1539 may be administered every 24 hours (±1 hour) until the subject is either discharged from the hospital or until IV study drug analgesia is no longer clinically indicated. Subjects may receive up to a maximum of three doses of N1539.

Subjects will receive non-NSAID standard of care analgesia according to the standard practice of the institution based upon the procedure type (Section 5.13). Other standard of care practices associated with the surgical procedure, which are not specially defined in the protocol, will be carried out according to the investigator's clinical practice and in accordance with institutional standards.

Subjects will be discharged from the study unit when deemed appropriate by the investigator based on clinical status. Subjects who are discharged from the study unit the same day as surgery will return to the study unit the next day (Day 2) in sufficient time to allow for collection of the 24-hour PK sample.

Subjects will have a follow-up visit at the clinical site 7 days after the last dose of study drug (LSD+7) and will be assessed primarily for adverse events (AEs) and wound healing. A final telephone interview will be conducted with the subject's parent or legal guardian 28 days after the last dose of study drug (LSD+28) to assess for AEs. After this follow-up telephone interview is completed, subjects are considered to have completed the study.

4. STUDY POPULATION

Subjects must meet all inclusion criteria specified in Section 4.1 and none of the exclusion criteria specified in Section 4.2 of the protocol to be eligible for participation in this study.

4.1. Inclusion Criteria

To be eligible for inclusion into this protocol, subjects must:

1. Be a male or female 2 to <17 years of age before dosing on Day 1.
2. Be eligible for elective surgery that will be performed according to standard surgical technique under appropriate anesthesia.
3. Be premenarche or have confirmed negative urine pregnancy testing before surgery on Day 1, if an adolescent female of childbearing potential.
4. Be willing and able to cooperate with all the requirements of the study.
5. Be able to speak and understand English or Spanish.
6. Have a legally authorized representative (e.g., parent, guardian) who is able to read, speak, and understand English or Spanish and who will voluntarily sign and date a parental permission/informed consent form that is approved by the Institutional Review Board/Independent Ethics Committee/Human Research Ethics Committee (IRB/IEC/HREC).
7. Be willing to sign an assent (if appropriate dependent upon the subject's age, understanding, and IRB requirements), before the conduct of any study procedure.

4.2. Exclusion Criteria

A subject will be excluded from study participation if prior to surgery he/she:

1. Has a known allergy or hypersensitivity to meloxicam, aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), or any excipient of N1539.
2. Has a known bleeding disorder that may be worsened with the administration of an NSAID.
3. Is undergoing cardiothoracic surgery.
4. Has used meloxicam within 7 days before the surgical procedure on Day 1.
5. Is currently taking any medication, food, beverage, or herbal supplement that interferes with CYP3A4 or CYP2C9 metabolism and is unable to discontinue this medication, food, beverage, or herbal supplement at least 14 days before administration of N1539 on Day 1 and continuing through collection of the final PK sample on Day 2 (24 hours after administration of N1539).
6. Is unable to discontinue any medication (prescription or over-the-counter [OTC]) within 5 half-lives of the specific medication (or within 48 hours if the half-life is unknown) before administration of N1539 on Day 1. The only exceptions are oral contraceptives, acetaminophen, and those medications utilized during the preparation of the subject for surgery.

7. Has evidence of a clinically significant 12-lead electrocardiogram (ECG) abnormality as determined by the investigator.
8. Has participated in a clinical trial (investigational or marketed product) within 30 days before surgery.
9. Has any clinically significant medical history or clinical manifestations of significant cardiac, neurological, immunological, renal, hepatic, or hematological disease or any other condition that in the opinion of the investigator, substantially increases the risk associated with the subject's participation in the study or compromises the scientific objectives of the study.

4.3. Discontinuation of Subjects

4.3.1. Procedures for Withdrawal

A subject may withdraw his/her consent for study participation at any time or the investigator or sponsor may discontinue a subject from the study at any time if either determines that it is not in the subject's best interest to continue study participation.

Subjects who receive at least one dose of study drug and are subsequently withdrawn from treatment will be encouraged to complete the discharge assessments prior to leaving the hospital/facility and to complete all follow-up assessments (i.e., LSD+7 visit and LSD+28 telephone interview). The date the subject is withdrawn from treatment and/or the study and the primary reason for discontinuation will be recorded.

4.3.2. Replacement of Subjects

Subjects may be replaced as necessary to ensure that an adequate number of subjects within an age group have sufficient PK samples for the determination of plasma meloxicam levels at each of the four time points after N1539 dosing.

4.4. Lifestyle Guidelines

4.4.1. Confinement

Each subject will arrive at the study site on Day 1 with sufficient time to be prepared for the surgical procedure and for the investigator or qualified designee to confirm continued eligibility to participate in the study. Subjects will be discharged from the study unit when deemed appropriate by the investigator based on clinical status. Subjects who are discharged from the study unit the same day as surgery will return to the study unit the next day (Day 2) in sufficient time to allow for collection of the 24-hour PK sample (Section 6.3).

4.4.2. Diet

Prior to the surgical procedure, subjects will be allowed nothing by mouth (PO) starting at a time designated by the investigator. Adolescent females currently taking oral contraceptives will be allowed to take their medication before surgery with up to 60 mL of water. Post procedure dietary requirements will be at the discretion of the investigator.

5. TREATMENTS

5.1. Study Drug Administration

Appropriately qualified study personnel will prepare all doses of study drug according to subject age group. All doses of study drug will be administered as an IV bolus injection with the dose calculated from the Day 1 body weight measurement. Start time of IV push will be recorded. Additional details on study drug preparation and administration will be provided in the study specific pharmacy manual.

At the end of the surgical procedure (Hour 0, defined as the time of last suture, staple, or steri-strip placement) each subject will receive their first dose of N1539 according to age group as shown in Table 4. Additional doses of N1539 may be administered every 24 hours (±1 hour) until the subject is either discharged from the hospital or until IV study drug analgesia is no longer clinically indicated. Subjects may receive up to a maximum of three doses of N1539.

5.2. Identity of Study Drug

Meloxicam injection for IV use will contain: 30 mg meloxicam in each 1 mL of solution, as well as excipients including povidone, sodium deoxycholate (deoxycholic acid), sucrose, and water for injection.

5.3. Method of Assigning Subjects to Dosing

Subjects will receive N1539 according to their weight on Day 1 as shown in Table 4.

Table 4: N1539 Dosing Cohorts by Age Group

Age Group	Number of Subjects	N1539 Dose
Group 1: 12 to <17 years	N=30	0.6 mg/kg (not to exceed 30 mg) Q24H
Group 2: 7 to <12 years	N=30	
Group 3: 2 to <7 years	N=30	

5.4. Selection of Doses

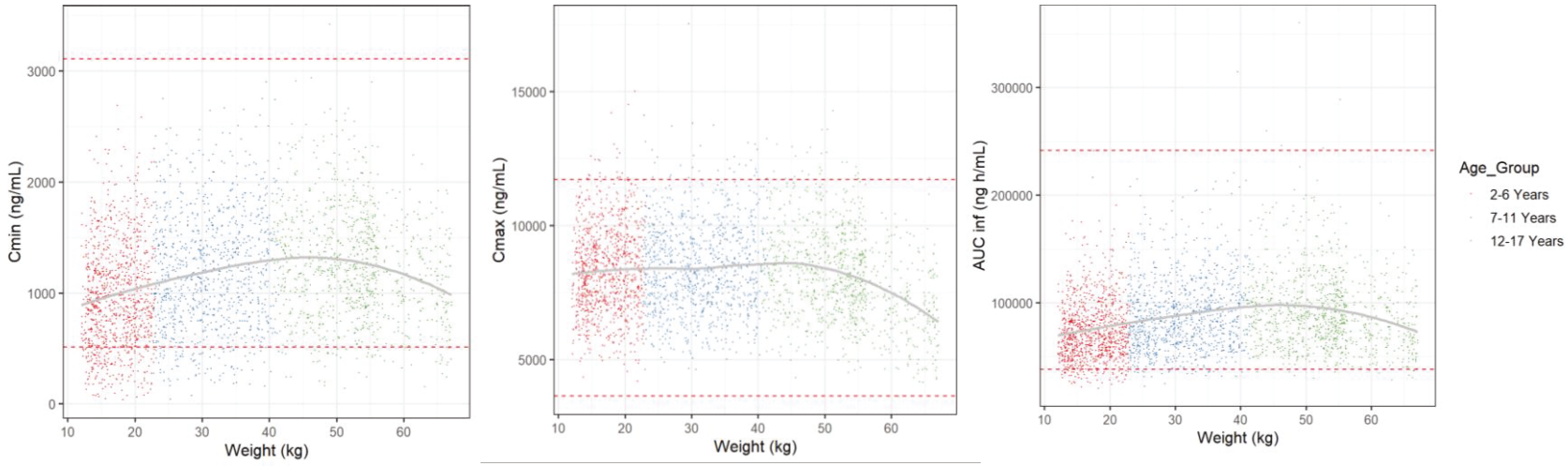
The exposure parameters of meloxicam in adults were used as a target to optimize pediatric dosing (full extrapolation approach), whereby exposure-response of efficacy and safety in pediatrics was assumed to be similar to adults. A population PK model was constructed with theoretical exponents (0.75 for central and peripheral clearances and 1 for central and peripheral volumes) based on the final PK model in adults.

The PK population model was used to simulate concentration-time profiles of meloxicam under various dosing scenarios for each age group and dose level (N=1000). Exposure parameters of meloxicam (C_{min} [24 hours post-dose], C_{max} [concentration at 5 minutes after IV bolus administration], and $AUC_{0-\infty}$) were derived and compared with the minimum and maximum values observed in adults (single administration of 30 mg of N1539). Based on these simulations, the dose level of 0.6 mg/kg (not to exceed 30 mg) was selected to provide meloxicam exposures most resembling those observed in adult subjects, with a low incidence of predicted exposures outside of the established range (see Figure 1). Under this dosing regimen, <3.5% of modeled

C_{max} results are predicted to exceed the range defined in adult PK subjects, while >83.5% of C_{min} results are predicted to fall within the defined range.

Additional details on the timing of PK sample collection and sample size calculations for each age group are provided in the modeling and simulations report (RECR-CSC-103).

Figure 1: Modeling Results for N1539 in Pediatric Subjects – 0.6 mg/kg Q24H (Maximum 30 mg)



Color marks represent individual simulated C_{min}/C_{max}/AUC_{inf} datapoints (n=1000 simulated subjects/age group) and gray line represent LOESS (Locally weighted scatter-plot smoothing) on simulated data.

Red lines are the threshold limits associated with a 30 mg single IV regimen dose overall the studies in adults (see Report RECR-CSC-103 for additional details of model construct and assumptions):

- C_{min}: minimum (513 ng/mL) and maximum (3110.0 ng/mL)
- C_{max}: minimum (3640 ng/mL) and maximum (11700.0 ng/mL)
- AUC_{inf}: minimum (38100 ng*h/mL) and maximum (241492.5 ng*h/mL)

5.5. Selection of Timing of Dose

At the end of the surgical procedure (Hour 0, defined as the time of last suture, staple, or steri-strip placement) each subject will receive their first dose of N1539. Additional doses of N1539 may be administered every 24 hours (±1 hour) until the subject is either discharged from the hospital or until IV study drug analgesia is no longer clinically indicated. Subjects may receive up to a maximum of three doses of N1539.

5.6. Dosing Within Age Group

After the last subject within an age group completes the follow-up visit (LSD+7), the safety committee will review all PK and safety data through LSD+7 and make a recommendation as to whether it is safe to allow dosing to proceed in the next youngest age group.

5.7. Blinding and Unbinding of Study Drug

This is an open-label study. All doses of study drug will be prepared by an appropriately qualified member(s) of the healthcare team at the research center according to the subject's age group.

5.8. Treatment Compliance

Qualified study personnel will administer each dose of study drug. The exact date and time each dose is administered will be recorded in the subject's eCRF.

5.9. Drug Accountability

The investigator (or qualified designee) will sign for study drug when it is received. Study drug must be handled and stored as described and dispensed only to those subjects formally entered into the study.

At the completion of the study, and after reconciliation of all delivery and usage records, any unused study drug supplied by the sponsor will be returned to the sponsor (or designee) or destroyed per written instructions from the sponsor.

5.10. Packaging, Labeling, and Storage

Study drug will be provided in study labeled packaging for preparation for use in this study. N1539 will be provided in single use vials containing 30 mg per mL.

Directions for preparation of study drug will be provided as pharmacy instructions prior to initiation of the study.

Study drug should be stored at the study site at 20° to 25°C (68° to 77°F), although a range of 15ºC to 30ºC (59ºF to 86ºF) will be permitted. Study drug should be stored protected from light.

All study drug at the study site(s) should be stored in a locked area with restricted access. A temperature log or chart should be maintained to monitor the storage environment at the study site.

5.11. Prior and Concomitant Medications

No prescription or nonprescription drugs including vitamins and supplements are allowed within 5 half-lives of the specific medication (or within 48 hours if the half-life is unknown) before administration of N1539 on Day 1.

The only exceptions are oral contraceptives, acetaminophen, and those medications utilized during the preparation of the subject for surgery.

All medications and other treatments taken by subjects within 7 days before administration of study drug on Day 1 and through the LSD+ 7 follow-up visit will be recorded in the eCRF.

5.12. Prohibited Medications

Any medication that interferes with CYP3A4 (e.g., azithromycin, clarithromycin, phenytoin) or CYP2C9 (e.g., metronidazole, sulfamethoxazole, barbiturates) metabolism is prohibited within 14 days before administration of N1539 on Day 1 and continuing through collection of the final PK sample on Day 2 (24 hours after the initial dose of N1539).

5.13. Analgesic Medications

Subjects will receive standard of care analgesic medications according to standard practice of the investigational site based on surgery type at the discretion of the investigator for the management of pain. Other NSAID medications are prohibited until 24 hours after the last dose of N1539. Subjects in the PK group who receive only one dose of N1539 are prohibited from receiving other NSAIDs until after collection of the 24-hour PK sample on Day 2.

5.14. Concomitant Interventions and Procedures

All interventions or procedures, whether diagnostic or therapeutic, will be recorded through LSD+7, along with time, date, and reason for the intervention or procedure. If an intervention or procedure is implemented after LSD+7 to treat an AE, the AE must be recorded along with all relevant information, including intervention and/or procedure.

6. STUDY PROCEDURES

6.1. Demographic Assessments

6.1.1. Demographics

Demographics information including age, gender, ethnicity, and race will be collected during the screening visit.

6.1.2. Medical History

During the screening period, the investigator or qualified designee will obtain a medical history from the subject's legally authorized representative that includes relevant diagnoses and/or procedures/therapies with onset/resolutions dates.

Medical history will be updated with any relevant information before the surgical procedure on Day 1.

6.1.3. Physical Examination

During the screening visit and during follow-up (LSD+7), the investigator or qualified designee will perform an age-appropriate physical examination on each subject. Height and body weight will be measured and recorded at screening. Body weight will be measured and recorded again before surgery on Day 1 for use in dose calculation.

6.2. Safety Assessments

6.2.1. Electrocardiograms

Safety ECGs (standard digital 12-lead ECGs) will be recorded at screening and during the follow-up visit on LSD+7 and evaluated by the investigator as 'normal', 'abnormal not clinically significant' or 'abnormal clinically significant'. The investigator will provide an explanation for all ECG findings that are considered abnormal. No interval measurements will be collected, and the ECG tracings will not be collected for data management.

The screening visit ECG will be used to exclude subjects with a clinically significant abnormal ECG.

6.2.2. Clinical Laboratory Testing

Adolescent girls of childbearing potential will have a urine pregnancy test before surgery on Day 1. Results must be available and negative before the subject can receive N1539.

Blood samples for routine hematology and chemistry laboratory testing will be collected during follow-up (LSD+7). Additional clinical laboratory testing will be at the discretion of the investigator and in accordance with institutional standards. Any clinically significant laboratory value after study drug administration on Day 1 should be captured as an AE at the discretion of the investigator.

6.2.3. Vital Sign Measurements

Vital signs including blood pressure, pulse, respiratory rate, and body temperature will be collected before surgery on Day 1, before hospital discharge, and at the LSD+7 follow-up visit.

Vital signs measurements during the intraoperative and postoperative inpatient periods will be collected at the discretion of the investigator and in accordance with institutional standards.

6.2.4. Wound Healing Assessment

Before hospital discharge and during the follow-up visit (LSD+7), the investigator or qualified designee will rate his/her satisfaction with wound healing using an 11-point scale (0-10) where a score of 0 is "completely unsatisfied", and a score of 10 is "completely satisfied".

6.2.5. Telephone Interview on LSD+28

Qualified study staff will conduct a telephone interview with the subject's parent or legal guardian on LSD+28 to assess for adverse events.

6.3. Pharmacokinetic Assessments

6.3.1. Sample Collection

Whole blood (1.5 mL per time point) will be collected in evacuated collection tubes treated with K2EDTA. Please refer to the laboratory manual for details.

Subjects included in the PK group (N=12 per age group) will have samples collected for PK analysis any time before administration of the first dose of study drug on Day 1, and at 5 minutes (±1 minute), 1 hour (±5 minutes), 3 hours (±5 minutes), and 24 hours (±10 minutes) after the first dose. The Hour 24 sample will be collected before administration of the second dose of study drug. Subjects in the PK group who are discharged from the study unit on the same day as surgery will return to the study unit the next day (Day 2) in sufficient time to allow for collection of the Hour 24 PK sample. A total of 7.5 mL of whole blood will be collected.

6.3.2. Processing, Storage, and Shipping of Pharmacokinetic Samples

Immediately after the collection of each sample, the collection tube will be gently inverted and then placed in wet ice. Within 30 minutes of withdrawal, the tubes will be centrifuged at about 2,000 × gravity for 10-15 minutes to separate the cells from the plasma. No aids for separation will be used. Two aliquots (approximately ≥0.3 mL each) of plasma will be transferred from each sample with clean pipettes and placed in 2 polypropylene storage tubes in equal volumes.

The storage tubes will be labeled with the following information: protocol number, subject number, period number, dose number and relative time of sample (e.g., Hour 1), and biologic matrix to be analyzed (e.g., plasma). Within 60 minutes of the collection time, the storage tubes will be placed into a freezer at –70ºC or below; they will remain in the freezer until shipped.

At a time designated by the sponsor, the samples will be packed with sufficient dry ice to keep them frozen for at least 48 hours and shipped to the analytical laboratory. On the day prior to shipment, clinical staff will notify (via telephone or email) the analytical laboratory of the pending shipment.

6.4. End of Study

The end of study is when the last subject's parent or legal guardian completes the LSD+28 telephone interview.

6.5. Assessments by Visit

6.5.1. Screening Period (Day -28 to Day -1)

Subjects meeting the eligibility criteria listed in Section 4 may be enrolled in the study after the nature and purpose of the protocol have been explained to the subject's legally authorized representative (e.g., parent, guardian) and they have voluntarily granted written informed consent for the subject to participate. Assent will also be obtained when appropriate based upon the subject's age and understanding. All subjects will have a screening evaluation within 28 days before the initial dose of study drug on Day 1.

After informed consent/assent is obtained, the following will be assessed and documented during the screening visit:

1. Review of inclusion/exclusion criteria eligibility (Section 4.1 and Section 4.2)
2. Demographics and medical history (Section 6.1.1 and Section 6.1.2)
3. Review of prior/concomitant medications/procedures (Section 5.11)
4. Physical examination including height, weight (Section 6.1.3)
5. 12-lead ECG (Section 6.2.1)
6. Serious adverse events (Section 7.2)

6.5.2. Inpatient Period

6.5.2.1. Surgical Procedure (Day 1)

6.5.2.1.1. Preoperative

The following will be assessed and documented preoperatively:

1. Update medical history (Section 6.1.2)
2. Concomitant medications/procedures (Section 5.11)
3. Body weight
4. Vital sign measurements (Section 6.2.3)
5. Urine pregnancy test for adolescent girls of childbearing potential (Section 6.2.2)
6. Establish continued eligibility for treatment
7. Serious adverse events (Section 7.2)

6.5.2.1.2. Intraoperative

The following will be assessed and documented intraoperatively:

1. Concomitant medications/procedures (Section 5.11)
2. Vital sign measurements (Section 6.2.3)
3. Surgical procedure according to the investigator's clinical practice and in accordance with institutional standards
4. Whole blood sample collection for meloxicam plasma concentrations (PK participants only; Section 6.3)
5. Administration of first dose of study drug at the end of the surgical procedure (Hour 0, defined as the time of last suture, staple, or steri-strip placement) according to age group (Section 5.1).
6. Adverse events after administration of N1539 (Section 7)

Upon completion of surgery, subjects may be transported to a post anesthesia care unit (PACU) until they are deemed ready for transport to their hospital room or to home.

6.5.2.2. Postoperative

The following will be assessed during the postoperative period as follows:

1. Concomitant medications/procedures (Section 5.11)
2. Vital sign measurements (Section 6.2.3)
3. Whole blood sample collection for meloxicam plasma concentrations (PK participants only; Section 6.3)
4. Administration of study drug until IV study drug analgesia is no longer clinically indicated (Section 5.1)
5. Administration of analgesic medication per institution standard of care (Section 5.13)
6. Adverse events (Section 7)

6.5.3. Hospital Discharge

Subjects will be discharged from the study unit when deemed appropriate by the investigator based on clinical status. The following will be assessed before hospital discharge:

1. Concomitant medications/procedures (Section 5.11)
2. Vital sign measurements (Section 6.2.3)
3. Administration of study drug at the discretion of the investigator (Section 5.1)
4. Administration of analgesic medication per institution standard of care (Section 5.13)
5. Wound healing assessment (Section 6.2.4)
6. Adverse events (Section 7)

Subjects in the PK group who are discharged from the study unit the same day as surgery will return to the study unit the next day (Day 2) in sufficient time to allow for collection of the 24-hour PK sample. Adverse events will also be assessed at this time.

6.5.4. Follow-up Visit (LSD+7)

Subjects will visit the clinical site and the following will be assessed and documented during the follow-up visit:

1. Concomitant medications/procedures (Section 5.11)
2. Physical examination (Section 6.1.3)
3. Vital sign measurements (Section 6.2.3)
4. 12-lead ECG (Section 6.2.1)
5. Clinical laboratory testing (Section 6.2.2)
6. Wound healing assessment (Section 6.2.4)
7. Adverse events (Section 7)

6.5.5. Postoperative Telephone Interview (LSD+28)

Qualified study staff will conduct a telephone interview with the subject's parent or legal guardian on LSD+28 to assess for adverse events. Following this interview subjects may be discharged from the study.

6.6. Discussion and Justification of Study Design

Study BDX-20-002 will be an open label study to evaluate the safety and PK of N1539 in children 2 to <17 years of age who are undergoing surgery.

Oral meloxicam (Mobic) has been in clinical use since 2000 and is currently approved at a dose of 7.5 mg daily for the relief of signs and symptoms of pauciarticular and polyarticular course juvenile rheumatoid arthritis in children ≥60 kg.

Following single dose administration of oral meloxicam (0.25 mg/kg), and after achieving steady-state (0.375 mg/kg/day), there was a general trend of approximately 30% lower exposure in younger children (2 to 6 years old) as compared to older children (7 to 16 years old). The older children had exposures similar (single-dose) to or slightly lower (steady-state) to healthy adults, when using AUC values normalized to a 0.25 mg/kg dose. Mean elimination half-life after administration of oral meloxicam was 15.2 hours and 13.0 hours for younger and older children, respectively, compared to approximately 20 hours in healthy adults. The PK of oral meloxicam has not been assessed in children <2 years of age.

It is hypothesized that the IV formulation of meloxicam will provide children with pain relief in the immediate postoperative period and will be safe and well tolerated based on data from the 1426 adults who received at least one dose of N1539 at doses ranging from 5 mg to 60 mg in the Phase 2/3 clinical program (Section 1.3).

To ensure the safety of subjects, enrollment in this study will start with the oldest age group (12 to <17 years) and will continue in a step-wise fashion until appropriate doses are established for all three pediatric age groups (12 to <17 years, 7 to <12 years, 2 to <7 years). After all subjects within an age group have completed the LSD+7 follow-up visit, PK and safety data including plasma meloxicam levels, adverse events, concomitant medications, medical history, vital signs,

and ECGs will be reviewed by the safety committee who will then provide a recommendation as to whether it is safe to proceed with dosing in the next youngest age group.

Modeling and simulations were performed to support the PK elements of the study design (i.e., number of PK samples collected, timing of PK sample collection, and number of PK subjects in each age group). Additional details on dose selection are provided in Section 5.4, with additional details around the timing of PK sample collection and sample size calculations for each age group provided in the modeling and simulations report (RECR-CSC-103). The current study design is expected to result in a robust understanding of PK parameters of meloxicam IV in each age group.

Meloxicam has a history of use in pediatric patients with oral administration. Enrollment in the current study includes additional subjects in each age group to provide a larger safety population. The safety sample size is consistent with similar pediatric protocol designs in pediatric acute pain/postoperative populations (NCT03682302, NCT01982539, NCT02287350, NCT02424578).

7. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

7.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE may be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered causally associated with the use of the study drug. Any abnormal laboratory value deemed clinically significant by the investigator, regardless of causal relationship, must be reported as an AE.

Examples of an AE include the following:

- Significant or unexpected worsening or exacerbation of the condition or indication under study
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency or intensity of the condition (e.g., abnormal physical examination finding)
- Signs, symptoms, or clinical sequelae of a suspected interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of the study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE, unless nonserious or serious sequelae occur)

The following examples are not considered AEs:

- Medical or surgical procedure (e.g., endoscopy, appendectomy), although the condition that leads to the procedure is an AE
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) (including laboratory values) present or detected at the start of the study that do not worsen
- The disease or disorder being studied, or expected progression, signs, or symptoms of the disease or disorder being studied, unless they become more severe or occur with a greater frequency than expected for the subject's condition

All AEs, whether volunteered, elicited, or noted on physical examination, and regardless of causality, will be assessed and recorded in the eCRF beginning after administration of study drug through end of the study (i.e., LSD+28).

7.2. Definition of a Serious Adverse Event

A SAE is defined as any event that meets the following criteria:

- Results in death

- Is immediately life-threatening (i.e., presents an immediate risk of death from the event as it occurred; this does not include an AE had it occurred in a more serious form may have caused death).
- Results in persistent or significant incapacity or substantial disruption of the ability to perform normal life functions.
- Results in hospitalization.
- Results in prolongation of an existing hospitalization.
- Is a congenital anomaly or birth defect (in the offspring of a subject using the study drug regardless of time to diagnosis).
- Is considered an important medical event.

Medical and scientific judgment should be exercised in determining whether an AE is serious when considering important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require medical or surgical intervention to prevent any of the outcomes listed that define a SAE. Examples of such medical events that may also be considered serious include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline does not meet the definition of a SAE.

Social or convenience admission to a hospital or prolongation of a hospitalization for social or convenience reasons not associated with the occurrence of an AE does not meet the definition of a SAE.

SAEs will be assessed and recorded in the eCRF after the signing of informed consent through the end of the study (i.e., LSD+28). If an investigator becomes aware of a SAE or death that occurs more than 30 days after the subject receives study drug and the investigator considers the event to be related to the study drug, he/she is obligated to report the SAE to the sponsor.

7.3. Recording and Evaluating Adverse Events and Serious Adverse Events

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, or other clinical information. In such cases, the diagnosis, not the individual signs or symptoms, should be documented as the AE or SAE.

7.3.1. Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study, using his or her clinical judgment. The intensity of each AE and SAE recorded in the eCRF should be assigned to one of the following categories:

- Mild: an event that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities

- Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: an event that prevents normal everyday activities

An AE that is assessed as severe should not be confused with a SAE. Severity is a term used to describe the intensity of a specific event, and both AEs and SAEs can be assessed as severe. The event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as serious, which is based on the subject's or event's outcome or on action criteria usually associated with events that pose a threat to a subject's life or functioning (see Section 7.2).

7.3.2. Assessment of Causality

The investigator must record the causal relationship of each event in the eCRF, and additionally for SAEs, on the SAE reporting form. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an AE.

- Definitely Related: An AE has a strong temporal relationship to the study drug. The AE is most likely explained by study drug. Dechallenge and rechallenge (if possible) are positive. The AE is consistent with a known response to the study drug. Another etiology is unlikely or significantly less likely.
- Probably Related: An AE has a strong temporal relationship to the study drug. The AE is more likely explained by study drug than by another cause. Dechallenge (if performed) is positive.
- Possibly Related: An AE has a reasonable temporal relationship to study drug. The AE could have been due to another equally likely cause. Dechallenge is positive.
- Not Related: The subject did not receive the study drug OR the AE has no temporal relationship to study drug OR the AE has a much more likely alternate etiology OR the AE is due to an underlying or concurrent illness or effect of another drug.

Even in situations in which minimal information is available for the initial SAE report, it is important that the investigator always make an assessment of causality for every event before transmitting the SAE reporting form and completing the AE eCRF page(s). The causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his or her opinion of causality in light of follow-up information and amend the SAE reporting form and AE eCRF page(s) accordingly.

7.3.3. Assessment of Outcome

All AEs and SAEs must be followed until they are resolved, the condition stabilizes, the events are otherwise explained, or the subject is lost to follow-up. The investigator will assess the outcome of the event(s) by using the following terms:

- Resolved: The event resolved and the subject returned to baseline.
- Resolving: At last observation, the event was improving.

- Resolved with sequelae: The event resolved but the subject is left with residual problems (e.g., functional deficits)
- Not resolved: At the last observation, the event was unchanged.
- Unknown: There were no observations after the onset (initial observation or report) of the event, and the status of the event is unknown.
- Death (*Fatal)*: To be selected for the ***one*** AE, which in the judgement of the investigator was the ***primary*** cause of death.

7.4. Follow-up of Adverse Events and Serious Adverse Events

After the occurrence of an AE or SAE, the investigator is required to follow each subject proactively and provide further information on the subject's condition. All AEs and SAEs documented at a previous visit or contact that are designated as ongoing will be reviewed at subsequent visits or contacts until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up. Any additional events that are relevant to the ongoing event will be documented.

The investigator will ensure that follow-up information relevant to SAEs is provided to the sponsor and includes results of any additional laboratory tests or investigations, histopathologic examinations, or consultations with other healthcare professionals that serve to clarify the nature of the event, the cause of the event, or both.

New or updated information will be recorded on the originally completed SAE reporting form and entered into the eCRF pages, with all changes signed and dated by the investigator. The updated SAE reporting form should be resubmitted to the sponsor within the time frames outlined in Section 7.5.

7.5. Prompt Reporting of Serious Adverse Events to the Sponsor

Once the investigator determines that an event meets the protocol definition of an SAE, he or she must notify the sponsor within 24 hours.

ANY SAE OR ANY OUTCOME OF DEATH DUE TO ANY CAUSE, WHICH OCCURS DURING THE COURSE OF THIS STUDY, REGARDLESS OF RELATIONSHIP TO STUDY DRUG, MUST BE REPORTED TO THE SPONSOR IMMEDIATELY (within 24 hours).

COMPLETE THE SAE DETAILS REPORTING FORM AND FORWARD BY eMAIL TO THE FOLLOWING SPONSOR CONTACT:

Medical Safety Baudax Bio, Inc.
Telephone: 484-395-2440
eFax:
eMail:

In the initial eMail, the investigator must provide to the sponsor the following eCRF pages, completed to the greatest extent possible:

- AE record
- Medical history
- Prior and concomitant medications

Also, the following documents are to be forwarded: any laboratory results, diagnostic test results, or medical reports relevant to the SAE.

E-mail transmission is the preferred method to transmit SAE information. In rare circumstances and in the absence of e-mail capacity, notification by fax or telephone is acceptable, with a copy of the SAE reporting form sent by overnight mail. Initial notification via telephone does not replace the need for the investigator to complete the SAE reporting form and eCRF pages within the time frames outlined.

If the investigator does not have all information regarding an SAE, he or she must not wait to receive additional information before notifying the sponsor of the event. The form must be updated when additional information is received. Follow-up information received on all SAEs must be forwarded to the sponsor by using the same procedure and timelines as for an initial report.

7.6. Regulatory Reporting Requirements

The investigator must promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 7.5 “Prompt Reporting of Serious Adverse Events to the Sponsor.” The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that SAEs that are either unexpected or observed with increasing occurrence, be reported and legal obligations and ethical responsibilities regarding the safety of other subjects are met.

For the purposes of investigational new drug (IND) safety reporting, expectedness of the SAE will be assessed by the sponsor. A SAE is considered unexpected if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

The sponsor will determine whether the SAE meets regulatory reporting criteria (ie, 7- or 15-day report) in compliance with local and regional law. If so, the sponsor (or the sponsor's representative) will report the event to the appropriate regulatory authorities. The sponsor will report SAEs to the central IRB/EC and the investigator will be report SAE to their local to institutional review board (IRB)/EC. Investigator letters are prepared according to sponsor policy and are forwarded to the investigators as necessary. An investigator letter is prepared for any SAE that is attributable to study drug, serious, and unexpected. The purpose of the investigator letter is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements regarding the product under investigation.

The investigator, or responsible person according to local requirements, must comply with requirements related to the reporting of SAEs to the IRB or IEC.

7.7. Special Reporting Situations: Pregnancy

Any subject who becomes pregnant during the study must discontinue further study drug administration and should be followed through delivery or termination of the pregnancy. A subject should be instructed to also notify the investigator immediately if she becomes pregnant within 30 days after receiving study drug. The sponsor must be notified of all pregnancies reported to the investigator (see Section 7.5 for contact information).

Any uncomplicated pregnancy that occurs in a subject during this clinical study will be reported for tracking purposes only. All subject pregnancies that are identified during or after this study, where the estimated date of conception is determined to have occurred within 30 days of receiving study drug need to be reported, followed to conclusion (delivery or termination), and the outcome reported, even if the subject is discontinued from the study. The investigator should report all pregnancies within 24 hours using the Pregnancy Report/Outcome Form, according to the usual timelines and directions for SAE reporting provided in Section 7.5. Monitoring of the pregnancy should continue until conclusion of the pregnancy; and follow-up detailing the outcome of the pregnancy submitted using the Pregnancy Report/Outcome Form.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs.

Any SAEs associated with pregnancy (e.g., congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE report form according to the usual timelines and directions for SAE reporting provided in Section 7.5.

8. STATISTICAL METHODOLOGY AND DETERMINATION OF SAMPLE SIZE

The following outlines some of the key elements of the data analysis approach. A formal statistical analysis plan (SAP) will be developed for this study in which statistical models, data derivation methods and rules will be described in detail.

8.1. Determination of Sample Size

Based on modeling and simulations, a study design with a PK population including 12 subjects per age group and five PK samples (i.e., pre-dose, 5 minutes and 1, 3, 24 hours after the initial dose) is expected to provide a robust estimation of clearance (CL) and volume of distribution (V) in pediatric subjects in each age group (RECR-CSC-103). This study design has a statistical power >80% for obtaining 95% confidence intervals for CL and V within the pre-defined 60% to 140% acceptance range (Wang 2012, FDA guidance UCM425885), which should enable accurate assessment of PK parameters following administration of meloxicam IV to pediatric subjects. Additional subjects will be enrolled into the safety population for each age group (N=30, inclusive of PK population subjects) to ensure adequate assessment of safety and tolerability.

8.2. Study Endpoints

For data analysis, baseline measures will be the last measurement taken before the subject receives the first dose of study drug.

8.2.1. Safety Endpoints

Safety endpoints include:

- incidence of AEs and SAEs
- incidence of clinically significant changes in vital signs
- incidence of clinically significant abnormal ECG findings
- investigator assessment of wound healing

8.2.2. Pharmacokinetic Endpoints

See Section 8.7.

8.3. General Considerations for Statistical Analysis

8.3.1. Test Hypothesis and P-Value Justification

No formal statistical analysis will be performed.

8.3.2. Procedures for Handling Missing Data

Unless indicated otherwise, no imputation will be done for missing data. However, AEs with missing severity assessments will be tabulated as “severe,” and AEs with missing relationship

assessments will be tabulated as "related" for the analysis; and the missing data will be presented in data listing as is.

8.3.3. Definitions for Assessment Windows

For data analysis, baseline measures will be the last measurement taken before the subject receives the first dose of study drug.

8.3.4. Derived Variables

Rules for derived variables will be described in the statistical analysis plan.

8.4. Analysis Populations

8.4.1. Intent-to-Treat (ITT) Population

The ITT population will include all subjects who are enrolled in the study, defined as informed consent signed by the parent or legal guardian and assent obtained from the child (as appropriate) and all eligibility criteria met. ITT subjects may or may not receive N1539.

8.4.2. Safety Population

The safety population will consist of all subjects who receive at least one dose of N1539. All safety evaluations will be based on the safety population.

8.4.3. Pharmacokinetic Population

The PK population will include all subjects who receive N1539 and have at least one PK sample above the LLQ for the determination of plasma meloxicam levels.

8.5. Statistical Methodology

8.5.1. Disposition

The summary tables will provide frequency counts for subject disposition (all treated subjects, subjects who completed the study, subjects who discontinued from the study, and reason for discontinuation) by dose group and study overall.

8.5.2. Demographics and Baseline Characteristics

The demographic summary will include descriptive statistics for age, sex, race, weight, height, CDC weight for age percentile, and other baseline characteristics of interest by dose group and study overall.

8.5.3. Protocol Violations

All protocol violations and deviations will be identified. Tabulation may be provided if data warrant.

8.5.4. Treatment Compliance

Study drug will be administered by designated study personnel to study subjects while subjects are confined to the study site. No formal summary of treatment compliance will be produced.

8.5.5. Prior and Concomitant Medications

All prior and concomitant medications will be tabulated for the overall study population. Prior and concomitant medications will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug classifications version 1Q2020 or higher.

8.6. Safety

Summary statistics will be prepared for measured safety for each dose group and study overall. Baseline data will be used for comparison to the data obtained during treatment and follow-up.

8.6.1. Extent of Exposure

Evaluation of the extent of exposure will be assessed via number of doses taken by dose group.

8.6.2. Electrocardiograms

ECG findings at each time point collected will be tabulated by dose group and study overall. An ECG listing will be prepared for subjects with at least one incidence of abnormal ECG results in the study. The time point where the abnormal ECG is observed will be flagged.

8.6.3. Vital Signs

Vital signs at each time point and change from baseline will be tabulated by dose group and study overall with descriptive statistics without inferential statistics. Number (%) subjects with clinically significant changes in vital signs post dosing will also be tabulated.

8.6.4. Clinical Laboratory Parameters

A listing of clinical laboratory findings will be provided.

8.6.5. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA; Version 23 or higher) will be used to classify all AEs with respect to system organ class and preferred term. An event is considered treatment emergent if the event onset date/time is on or after the first dose of study drug or if a prior condition is worsened after the first dose of study drug. AEs will be summarized by treatment group. AE summaries will be provided for all treatment emergent AEs, study drug related TEAEs, and serious TEAEs.

AEs that lead to premature discontinuation from the study or to death will be listed separately via data listings.

8.6.6. Wound Healing

Wound evaluation assessments (investigator satisfaction and surgical wound healing) at each time point collected will be summarized by dose group and study overall.

8.7. Pharmacokinetics

Pharmacokinetic endpoints for the determination of meloxicam concentrations in plasma will be

based on a population PK analysis in pediatric subjects who have at least one PK sample above the LLQ. Relevant covariates (i.e., body weight and estimated glomerular filtration rate) will also be integrated into the population PK analysis.

Individual parameters of N1539 in pediatric subjects will be obtained by fitting the models to the PK data. Primary PK endpoints (i.e., CL and V) will be generated with other parameters (i.e., $t_{1/2}$ and Vss).

The following exposure parameters will also be derived based on simulated rich concentration-time profiles using the actual dosing history and individual PK parameters: $AUC_{0-\infty}$, C_{max}, and C_{min}.

Individual concentrations will be summarized with descriptive statistics for each nominal time (i.e., predose, 5 min, 1, 3 and 24 hours after the IV administration) by dose group. Descriptive statistics of key parameters for N1539 (mean, standard deviation, coefficient of variation, standard error of the mean, sample size, minimum, maximum, and median) will be calculated for each dose group. In addition, geometric mean and geometric coefficient of variation will be derived. Additional details on the population PK analysis are provided in the analysis plan.

9. STUDY ADMINISTRATION

9.1. Regulatory and Ethical Considerations

9.1.1. Ethical Conduct of the Study

This study will be conducted according to the clinical research guidelines established by FDA Title 21 Code of Federal Regulations (CFR) Parts 50, 54, 56, and 312, ICH GCP and other regulations as applicable.

9.1.1.1. Institutional Review Board/Independent Ethics Committee

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the site's informed consent form, and any other information that will be presented to potential subjects (e.g., advertisements or information that supports or supplements the informed consent form) are reviewed and approved by the appropriate IRB or IEC. If the protocol, the informed consent form, or any other information that the IRB or IEC has approved for presentation to potential subjects is amended during the study, the investigator is responsible for ensuring that the IRB or IEC reviews and approves, where applicable, these amended documents prior to implementation of any changes. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form, including obtaining IRB or IEC approval of the amended form, before new subjects consent to take part in the study using the new version of the form.

For study sites with IECs that comply with ICH GCP, but not US FDA 21CFR Part 56, a waiver request will be submitted to the FDA. If granted, the FDA's letter documenting the waiver will be provided to the Investigator.

In addition, the investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC safety procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC and all other applicable regulations

9.1.1.2. Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Template informed consent forms will be provided by the sponsor but may be adapted to meet the needs of the institution. Final consent forms will be IRB/IEC approved and accepted by the sponsor.

In this study, the subject's parent or legal guardian will be asked to read and review the consent document. The investigator or designee will explain the study to the subject's parent or legal guardian and answer any questions that may arise. A verbal explanation will be provided in

terms suited to the subject's parent or legal guardian comprehension of the purpose, procedures, and potential risks of the study and of the rights of research subjects. The subject's parent or legal guardian will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subject's parent or legal guardian should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to let the subject participate. The subject's parent or legal guardian will sign the informed consent document prior to any procedures being done specifically for the study. The subject will also sign an assent (if appropriate dependent upon the subject's age, understanding, and IRB requirements) before the conduct of any study procedure

The subject's parent or legal guardian must be informed that participation of the subject is voluntary and that they may withdraw the subject from the study at any time, without prejudice. A copy of the informed consent and assent documents will be given to the subject's parent or legal guardian for their records. The informed consent process will be conducted and documented in the source document and the form(s) signed before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to the subject's parent or legal guardian that the quality of the subject's medical care will not be adversely affected if they decline to have the subject participate in the study.

9.1.1.3. Subject Confidentiality

Subjects will be assigned a unique identifier by the sponsor. Any subject records or data that are transferred to the sponsor will contain the identifier; subject names or any information which would make the subject identifiable will not be transferred. The investigator will keep a Master Subject List on which the identifier and full name, address, and telephone number of each subject are listed. The Master Subject List will be stored in a secure location at the site and will not be shared with the sponsor. It is the Investigator's responsibility to inform subjects as part of the informed consent process that representatives of the sponsor, FDA, or other regulatory agencies may review all records that support their participation in the study. The Investigator will comply with all privacy laws to which he/she is subject.

9.1.1.4. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9.2. Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checks of the data.
- Study monitors will perform ongoing source data verification to confirm that that data entered into the CRF by site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the current approved version of the protocol, ICH GCP, and all applicable regulatory requirements.

9.3. Study and Site Closure

If the sponsor, investigator, or officials from regulatory agencies discover conditions arising during the study that indicate that the study should be halted or that the study site should be closed, this action may be taken after appropriate consultation between the sponsor and investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- Discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- Submission of knowingly false information from the research facility to the sponsor, study monitor, or regulatory agencies
- Failure of the investigator to comply with GCP (eg, ICH guidelines, regulatory agency guidelines)
- Insufficient adherence to protocol requirements or an unacceptably high rate of missing, erroneous, or improperly collected data
- Evidence from the blinded data of sufficient technical problems with the study that one could believe with a high degree of certainty that subjects are being exposed to the investigational drug without a realistic expectation of evaluable data
- A decision on the part of the sponsor to suspend or discontinue testing evaluation or development of the product
- Failure of the investigator to enroll subjects into the study at an acceptable rate

9.4. Records Retention

9.4.1. Archiving of Study-Related Documents

Records related to this clinical study must be retained either for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The sponsor will notify the investigator as to when these documents no longer need to be retained for this use. No records may be transferred to another location or party without written notification to and approval of the sponsor.

9.5. Information Disclosure

9.5.1. Publication

For multicenter studies, the first publication or disclosure of study results shall be a complete, joint, multicenter publication or disclosure coordinated by Baudax Bio, Inc. Thereafter, any secondary publications will reference the original publication(s). If no multicenter publication is submitted for publication within 18 months of study database hard lock, then the site shall be free to disclose its own results, subject to sponsor rights under the written contract executed for the conduct of the study. Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors authorship requirements.

Before submitting material for publication, presentation, or use for instructional purposes, or before otherwise disclosing the study results generated by the site (collectively, a "publication"), the investigator shall provide Baudax Bio, Inc. with a copy of the proposed publication and allow Baudax Bio, Inc. a period of at least 90 days to review the proposed publication. Proposed publications shall not include either Baudax Bio, Inc. confidential information (other than the study results) or the personal data (such as name or initials) of any subject.

At Baudax Bio, Inc.'s request, the submission or other disclosure of a proposed publication will be delayed a further 120 days to allow Baudax Bio, Inc. to seek patent or similar protection of any inventions, know-how, or other intellectual or industrial property rights disclosed in the proposed publication.

Where a written contract is executed for the conduct of the study, that contract's publication provisions will supersede the language in this section.

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APPENDIX A: STUDY ASSESSMENTS: PROTOCOL BDX-20-002

Assessment	Screening	Surgery (Day 1) Through Hospital Discharge[a] or LSD +1, Whichever Occurs First				Follow-up Visit	Telephone Interview
	Days -28 to Day -1	Preoperative	Intraoperative (Start to End of Surgery)	Postoperative Hour 0 Through Hospital Discharge[a] or LSD +1	Hospital Discharge[a]	LSD+7 (± 1 day)	LSD+28 (± 3 days)
Informed consent/assent	X						
Eligibility assessment	X	X[b]					
Demographics	X						
Medical history	X	X[b]					
Prior/concomitant medications and procedures	X	X	X	X	X	X	
Physical examination	X					X	
Body weight	X	X[b]					
Height	X						
Vital signs (pulse rate, respiratory rate and BP)		X	X[c]	X[c]	X	X	
12-lead ECG	X					X	
Clinical laboratory testing						X	
Urine pregnancy testing		X[d]					
Pharmacokinetic sampling[e]			X	X			
Study drug administration[f]			X	X	X		
Analgesic medication[g]				X	X		
Investigator satisfaction with wound healing					X	X	
Adverse events[h]	X	X	X	X	X	X	X
Discharge from study							X

ECG=electrocardiogram; LSD=last study dose

a Subjects will be discharged from the study unit when deemed appropriate by the investigator based on clinical status.

b Update before surgery.

c Vital sign assessments during the intraoperative and postoperative periods will be at the discretion of the investigator and in accordance with institutional standards.

d Before surgery in adolescent girls of childbearing potential only. Results must be negative before the subject can receive N1539.

e PK Group Only - Whole blood samples will be collected any time before administration of the first dose of study drug on Day 1 and at 5 minutes (±1 minute) and 1 hour (±5 minutes), 3 hours (±5 minutes), and 24 hours (±10 minutes; prior to administration of Dose 2) after Dose 1. Subjects who are discharged from the study unit on the same day as surgery will return to the study unit the next day (Day 2) in sufficient time to allow for collection of the Hour 24 PK sample.

f Dose 1 of study drug will be administered at the end of the surgical procedure (Hour 0, defined as the time of last suture, staple, or steri-strip placement). Additional doses of N1539 may be administered every 24 hours (±1 hour) until the subject is either discharged from the hospital or until IV study drug analgesia is no longer clinically indicated. Subjects may receive up to three doses of N1539.

g Subjects will receive non-NSAID standard of care analgesia according to the standard practice of the institution based upon the procedure type.

h Only serious adverse events will be collected before administration of the first dose of N1539.