Study Protocol Cover Page

Study Official Title: A Phase 1a Randomized, Double-blind, Placebo-controlled, Single Site, Single Ascending Dose Study of the Safety, Tolerability, and Pharmacokinetics of Kindolor Tosylate in Healthy Adults

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A Phase 1a Randomized, Double-blind, Placebo-controlled, Single Site, Single Ascending Dose Study of the Safety, Tolerability, and Pharmacokinetics of Kindolor Tosylate in Healthy Adults

Sponsor: Lohocla Research Corporation
Colorado Bioscience Park
[redacted]

Principal Investigator: Mark Wallace, MD
University of California San Diego
[redacted]

Data Management/ Monitoring: Fast-Track Drugs & Biologics, LLC
[redacted]

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CRF Part 46, 21 CFR Part 50, 21 CFR Part 56 and 21 CFR Part 312)
- International Conference on Harmonisation (ICH) E6

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

1. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Lohocla Research Corporation	
Name of Investigational Product: Kindolor Tosylate	
Name of Active Ingredient: Kindolor (DCUKA)	
Protocol Number: KIND-2022-01	
Study Title: A Phase 1a Randomized, Double-blind, Placebo-controlled, Single Site, Single Ascending Dose Study of the Safety, Tolerability, and Pharmacokinetics of Kindolor Tosylate in Healthy Adults	
Principal Investigator: Mark Wallace, MD	
Study Centers: University of California San Diego (UCSD)	
Study Period: ~ 6 months	**Phase of Development:** 1a
Objectives: **Primary:** The primary objective of the study is to determine the safety and maximum tolerated dose (MTD) of kindolor tosylate in healthy volunteers. **Secondary:** The secondary objective of the study is to determine the PK of kindolor tosylate by quantitating kindolor levels in plasma across a range of doses in healthy volunteers.	
Methodology: This is a Phase 1a, randomized, double-blind, single ascending dose study designed to assess the safety, tolerability, and PK of kindolor tosylate. Healthy male and female adults will be screened for eligibility by medical history, physical examination including height and body weight, vital signs, 12-lead electrocardiogram (ECG), clinical laboratory tests (amylase, lipase, chemistry, hematology, and coagulation tests, medical urinalysis, and infectious disease screen), urine drug screen for drugs of abuse, fecal occult blood tests (FOBT), and medication use. Females will have a pregnancy test. Using a dose escalating design, eligible subjects will receive randomly assigned enteric coated oral tablets of kindolor tosylate (100 mg and 300 mg strengths) or identically matched Placebo tablets in 4 cohorts of 8 subjects (6 kindolor tosylate subjects and 2 placebo subjects in each cohort). A sentinel cohort of 2 subjects (1 active and 1 placebo) will be dosed and closely monitored for at least 24 hours prior to dosing the remaining 6 subjects in each successive cohort. Ascending doses of kindolor tosylate include 100 mg (1 x 100 mg tablet), 300 mg (1 x 300 mg tablet), 900 mg (3 x 300 mg tablet), and 1800 mg (6 x 300 mg tablet). The safety data for each completed cohort will be reviewed by the UCSD Clinical and Translational Research Data and Safety Monitoring Board (DSMB) that will recommend continuation to the next cohort or stopping the study due to safety concerns. Eligible subjects will undergo intake procedures at the UCSD Clinical and Translational Research Institute Phase I unit on Study Day -1 (the day before the start of dosing) and will complete final screening and baseline evaluations including baseline assessments. On Study Day 1, subjects will receive the study drug after an overnight fast (about 8 hours) with no food allowed until 4 hours after dosing. Study drug tablets will be administered with 240 mL of water. Subjects will remain in the unit for at least an additional 48-hours for safety assessments and blood collections to determine plasma levels of kindolor. Pre-dose assessments will be conducted prior to administration of study drug on Study Day 1. Blood for PK will be collected ~ 15 minutes prior to dosing, then at 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, and 48 hours after dosing. Safety will be assessed by collecting adverse events (AEs), vital signs, physical examination, ECG, FOBT, Stool Consistency Questionnaire, GI Symptoms Checklist, and clinical laboratory tests (amylase, lipase, chemistry, hematology, coagulation tests, pregnancy tests, and urinalysis). AEs will be assessed daily after the start of dosing, with closer evaluations in the	

4-hour period after the start of dosing. Sitting (3 minutes) vital signs will be taken during screening, at clinic check in, pre-dose, then at 15, 30, 60 minutes and 2, 4, 6, 12, 24, and 48 hours post dose. A 12-lead ECG will be obtained prior to dosing, then at 2, 6, 12, 24, and 48 hours post dose. When vital signs or ECG are scheduled at the same time as a PK blood draw, these assessments will be performed before drawing any blood. The FOBT will be performed at screening, clinic intake on Day -1, pre-discharge on Day 3, and at follow-up on Day 7. Subjects will return for a final follow-up visit 7±2 days after discharge for a final safety assessment including vital signs, ECG, AEs, FOBT, Stool Consistency Questionnaire, GI Symptoms Checklist, and clinical laboratory tests.

Number of Subjects (Planned): 32

Main Inclusion/Exclusion Criteria: Healthy male or female volunteers, aged 18-to-55 years, with body mass index (BMI) between 18 and 32 kg/m^2 (inclusive)

Investigational Product, Dosage, and Mode of Administration: Kindolor tosylate will be supplied as enteric coated tablets containing 100 mg and 300 mg drug product for oral administration. Tablets will be consumed orally with 240 mL of water under observation by a study staff member.

Reference Therapy, Dosage, and Mode of Administration: Placebo enteric-coated tablets identically matched to investigational product tablets will be consumed orally. Enteric coated tablets, with an equal amount of Prosolv SMCC replacing the drug product, will be provided as the placebo.

Duration of Study: Each subject will participate in the study for up to 58 days for females and 120 days for males, including up to 30 days for screening, 4 days and 3 nights residing in the Phase I unit, with one follow-up visit 7 ± 2 days after discharge, with a telephone call check at 28 days after dosing for females and 90 days after dosing for males for a verification contraceptive practices, and conformance with agreement not to donate ova, breastfeed, or donate sperm during this period.

Criteria for Evaluation:

Safety: AEs, physical examinations, clinical laboratory data, ECG, FOBT, Stool Consistency Questionnaire, GI Symptoms Checklist, urine output over 24 hours, and vital signs.

Pharmacokinetics: AUC_∞, AUC_t, C_{max}, t_{max}, λ_z, $t_{½}$

Statistical Methods (Data Analysis):

Analysis Populations:

Safety: The safety population will include all subjects who received a dose of investigational product.

PK: The PK population will include subjects who received kindolor tosylate and had sufficient plasma concentrations to reliably calculate PK parameters.

Sample Size: The cohort size of 6 subjects receiving the active drug is generally accepted for first-in-humans clinical trials that provides a reasonable sample size for PK parameter estimates. Administration of kindolor tosylate to 6 subjects in each dose group provides a 47%, 62%, 74%, or 82% probability of observing at least 1 occurrence of any AE with a true incidence rate for a given dose group of 10%, 15%, 20%, or 25%, respectively. Furthermore, it is assumed that pooling the data for the subjects who received placebo (2 from each cohort) will provide an adequately sized control group.

Safety Analyses: The severity, frequency, and relationship of AEs to investigational product will be presented by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) grouping. Listings of each individual AE including start date, stop date, severity, relationship, outcome, and duration will be provided. GI AEs will also be summarized separately including stool consistency and presence/absence and severity of other symptoms according to the GI Signs and Symptoms Checklist or endoscopy results if applicable. Clinical chemistry, hematology, coagulation, urinalysis, FOBT, urine drug screen results, amylase, lipase and pregnancy test results

will be presented as summary statistics and change from baseline. Urine output for 24 hours will be presented as summary statistics per time period. In addition, change from baseline (shift tables) will also be presented for clinical chemistry, hematology, and coagulation data. Vital signs and ECG parameters will be presented as summary statistics and change from baseline. The proportions of ECG results considered clinically significant will also be provided. All data will be presented by treatment group. Placebo subjects from each cohort will be treated as one group for statistical analyses.

PK Analyses: The concentration-time profiles will be evaluated by non-compartmental analysis and will be displayed graphically by subject and by summary statistics by group. Calculations of parameters will be performed with Phoenix WinNonLin. The elimination rate constants (λ_z) will be estimated from the terminal log-linear decline in plasma concentrations and $t_{½}$ calculated as $0.693/\lambda_z$. Area under the plasma concentration curves (AUC) will be determined until the last time of a quantifiable plasma concentration (AUC_t) by the log/linear trapezoidal rule and to infinity (AUC_∞) based on the last plasma concentration and λ_z. The value of t_{max} will be the observed time of the highest plasma concentration, and C_{max} will be the plasma concentration at that time.

Baseline Descriptive Statistics:

Summaries of the characteristics of the subjects in each of the study groups at baseline will be prepared.

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3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
β-hCG	Beta-human chorionic gonadotropin
λ_z	terminal-phase exponential rate constant
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_∞	area under the plasma concentration-time curve from time 0 extrapolated to infinity
AUC_t	Area under the plasma concentration-time curve from time 0 to the time (t) of last quantifiable concentration (C_t)
BCRP	breast cancer resistance protein
BID	twice-a-day
BMI	body mass index
BUN	Blood urea nitrogen
C	Celsius
CAP	College of American Pathologists
CB2	Cannabinoid type 2
CBD	cannabidiol
CFA	Complete Freund's Adjuvant
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Act
C_{max}	maximum observed plasma concentration
CNS	central nervous system
COX	cyclooxygenase
COX-1	cyclooxygenase-1
COX-2	cyclooxygenase-2
CPK	creatinine phosphokinase
CYP2C9	cytochrome P450 2C9
eCRF	Electronic Case Report Form
EC_{50}	Half maximal effective concentration
ED_{50}	Half maximal effective dose
DCUKA-OH	Kindolor metabolic product: hydroxylation
DCUKA-gluc	Kindolor metabolic product: glucuronidation

Abbreviation	Definition
DCUKA-OH-gluc	Kindolor metabolic product: hydroxylation + glucuronidation
DDI	Drug-drug interaction
DOR	Delta Opiate Receptor
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EDMS	Electronic data management system
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FOBT	Fecal occult blood test
FSH	follicle-stimulating hormone
g	Gram
GABA	Gamma aminobutyric acid
$GABA_A$	Gamma aminobutyric acid type A
GCP	Good Clinical Practice
GI	Gastrointestinal
GLPs	Good Laboratory Practices
HAV-IgM	hepatitis A virus immunoglobulin M
HBsAg	hepatitis B surface antigen
HCV Ab	hepatitis C virus antibody
HED	Human Equivalent Dose
hERG	human ether-à-go-go-related gene
HIPAA	Health Insurance Portability Accountability Act
HIV	Human Immunodeficiency Virus
HIV Ab	HIV antibodies
HPMC	hydroxypropyl methylcellulose
hr	Hour
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonization
IND	Investigational New Drug
INR	International normalized ratio
ip	Intraperitoneal(ly)
IRB	Institutional Review Board
kg	Kilogram

Abbreviation	Definition
L	Liter
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MDMA	methylenedioxymethamphetamine
mg	Milligram
mL	Milliliter
μg	Microgram
mL	Milliliter
mM	Millimolar
NK1	Neurokinin 1
NMDA	N-methyl-D-aspartate
NOAEL	no-adverse-effects level
NSAIDs	non-steroidal anti-inflammatory drugs
PAM	positive allosteric modulator
PDN	painful diabetic neuropathy
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic
PT	Preferred term or prothrombin time
RBC	Red blood cell
RNA	ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SEM	Standard error of the mean
SNL	Spinal nerve ligation
STZ	streptozotocin
SOC	System Organ Class
THC	Tetrahydrocannabinol
t_{max}	observed time to reach maximum plasma concentration
$t_{½}$	apparent terminal exponential half-life
TRPV1	Transient receptor potential vanilloid type 1
VSNaC	Voltage sensitive sodium channel

Abbreviation	Definition
UCSD	University of California San Diego
UDP- UGTs	uridine diphosphate-glucuronosyltransferases
ULN	Upper limit of normal
U	Units
US	United States
WBC	White blood cell

4. INTRODUCTION

4.1. Chronic Pain

Chronic pain is estimated to affect 1/3 of the U.S. population and can negatively impact quality of life (Reuben-2015). Although normal pain in response to tissue damage is an important physiologic mechanism for keeping an organism out of harm's way, in some instances, the nervous system can undergo a metamorphosis that makes pain a constant component of life. The pharmacologic treatment of neuropathic or other chronic pain states has relied heavily on the use of opiates or their derivatives (Reuben-2015), all of which are associated with a plethora of attendant adverse effects (Chou-2015). More recently, pharmaceuticals, including gabapentin and pregabalin, which target the α2δ subunits of P-type and N-type voltage-sensitive calcium channels, and duloxetine, which targets norepinephrine and serotonin uptake, have reached prominence as treatments for chronic pain (Lunn-2014; Moore-2014; Schreiber-2015). However, opiates remain a mainstay for treatment of chronic pain. The use of opioids for pain treatment has resulted in what has been called an "epidemic" of opioid abuse, addiction, and lethal overdoses. Therefore, a significant effort continues to be made to generate new and better pain medications.

Many of these efforts have focused on targeting single molecular entities such as transient receptor potential vanilloid type 1 (TRPV1), neurokinin 1 (NK1), and cannabinoid type 2 (CB2) receptors (Hill-2000; Lehto-2008; Rahn-2009). However, targeting a single receptor, channel, or enzyme to control a complex physiologic system has been suggested to result in limited efficacy (Pang-2012). The systems that subserve chronic pain syndromes are well represented by network models, and it has been posited (Csermely-2005) that a partial inhibition of more than one target within a network can be more efficient than the complete inhibition of a single target.

During the process of sensitization leading to chronic pain syndromes, hyper-responsivity in the peripheral sensory system is followed by sensitization of neurons in the central nervous system (CNS) (Campbell-2006). There is increasing evidence for the role of peripheral mechanisms in chronic pain syndromes (e.g., Parada-2003; Christoph-2005; Villarreal-2005; Staud-2010; Ferrari-2014; Ma-2014; Yang-2014; Boada-2015), and some of the most well-established peripheral changes are up-regulation of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors (Du-2003; Jang-2004; Childers- 2007), and of voltage sensitive sodium channels (VSNaCs) (Wang-2002; Black-2004; Coggeshall-2004; Lai-2004; Dib-Hajj-2007; Levinson-2012). Such neuroadaptive events provide candidate targets for developing multi-target medications for treatment of chronic pain.

Lohocla Research Corporation is developing kindolor tosylate, a multi-target drug for the treatment of chronic inflammatory and neuropathic pain (Tabakoff-2016).

4.2. Kindolor Tosylate

4.3. Rationale for Studying Kindolor

Kindolor is designed to specifically target the network of entities that conduct and amplify pain signals that arise in the periphery and are transmitted to the CNS. Nonclinical studies support that kindolor may be an effective, non-addictive, and safe alternative to mu opiate receptor (MOR) agonists for treatment of chronic pain (hyperalgesia, allodynia) with minimal effects (allowing normal pain sensations) in an undamaged sensory system. Also, kindolor could be given in combination with opiates to reduce the dose of opiates by 3-5-fold in treating chronic pain conditions, thus reducing opiate side effects, addictive potential, tolerance, and mortality. Another possible indication for kindolor is to prevent the development of chronic pain (e.g., cancer chemotherapy-induced neuropathic pain and chronic inflammatory pain).

4.4. Mechanism of Action

Kindolor was rationally designed to target systems that conduct sensory information from nociceptors and systems that transduce information between and within sensory neurons. At a

defined concentration range of <10 μM, kindolor significantly affects the function of multiple targets resident in peripheral sensory neurons. Kindolor does not engage a large number of other tested targets at concentrations ≤ 10 μM and demonstrates an excellent therapeutic index based on pharmacologic and toxicologic studies in animals (estimated therapeutic index in rats ≥18). The targets identified through *in vitro* target binding and functional studies were the $Na_v1.7$ and $Na_v1.8$ VSNaCs, the NMDA receptor, the DOR, and the $GABA_A$ receptor. There is ample evidence from the literature, that these receptors/ion channels are all contributors to development and maintenance of the peripheral sensitization component of chronic pain syndromes (Faber-2012, Ferrari-2014, Du-2017, François-2018, Hameed-2019, Xiao- 2019, Quirion-2020, Lee-2012). Kindolor does not accumulate in brain and does not display CNS-mediated behavioral effects. An interesting observation regarding the NMDA and VSNaC receptors/ion channels that are targets for kindolor is that there is evidence that these targets are up-regulated in the course of development of chronic pain and the direction of kindolor's action (antagonist) would oppose the effects (hyperalgesia) generated by the up-regulation of the target NMDA and VSNaC receptors/ion channels.

Kindolor is an agonist at the DOR, which is another node in the chronic pain network. DORs are expressed along the length of sensory neurons and have been well demonstrated to localize in small diameter sensory neurons which also express $Na_v1.7$ and $Na_v1.8$. DOR activation can reduce signal propagation from the peripheral receptors (François-2018; Bigliardi-2006; Quirion-2020, Gaveriaux-Ruff-2011; Gendron-2016).

In addition, kindolor also acts as a PAM at $GABA_A$ receptors. Activation of the $GABA_A$ receptors in the DRG has been demonstrated to abrogate painful sensory stimuli traversing nociceptors through the DRG (Du-2017).

Kindolor's action at the $Na_v1.7$ and $Na_v1.8$ sodium channels, NMDA receptor, $GABA_A$ receptor, and the DOR can dampen the increased signaling which occurs during peripheral sensitization in chronic pain states. Kindolor is a good example of a drug directed at a network rather than a singular target. In this way, a modest effect at a number of the network components can produce a more profound effect than a maximal effect at any one target of the network (Boezio-2017, Ramsay-2018).

To investigate the ability of kindolor to alleviate chronic pain, multiple *in vivo* chronic pain models in rodents were utilized. Each *in vivo* nonclinical model of chronic pain syndrome has had its detractors (Clark-2016) and variations in protocol within a particular model can lead to disparate results (Miller-2015). Therefore, testing of the anti-hyperalgesic effects of kindolor was performed in several models of pain in two species (rats and mice). The models included: the Complete Freund's Adjuvant (CFA) and the Freund's Incomplete Adjuvant plus *Mycobacterium butyricum* models of inflammatory pain in rats; the Formalin model of acute and "chronic" inflammatory pain in mice; the Spinal Nerve Ligation (SNL) Model (constriction-induced neuropathy) in rats; the Streptozotocin (STZ) model of painful diabetic neuropathy (PDN) in rats; and the cisplatin cancer chemotherapy-induced neuropathy model in rats.

[redacted]

Kindolor when combined with CNS acting analgesics (opioids, NSAIDs) produced supra-additive or synergistic effects on reduction of chronic pain. Another notable aspect of kindolor's action was its demonstrated ability to prevent the development of chronic pain (allodynia) in both the cisplatin chemotherapy-induced neuropathy model and the CFA-induced inflammatory pain model. This provides an indication that, if given early after a damaging insult to the peripheral nervous system, kindolor could ameliorate the early stages of increased sensitivity to painful stimuli and if kindolor administration is continued, kindolor could prevent a transition to the more severe stages of a chronic pain syndrome. Notably, chronic exposure of kindolor did not produce tolerance to kindolor's effect in a model of inflammatory pain.

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat inflammatory pain, and act by competitively inhibiting cyclooxygenase (COX), the enzyme responsible for mediating the conversion of arachidonic acid to prostaglandins (Zarghi-2011). Cyclooxygenase-1 (COX-1) is constitutively expressed in most tissues, including the stomach, whereas low levels of cyclooxygenase-2 (COX-2) protein and activity have been found in the human stomach. *In vitro* studies showed that kindolor did not significantly inhibit human COX-1 or human COX-2 activity suggesting that kindolor acts through a novel mechanism, which is distinctly different from that of NSAIDs.

4.5. Kindolor Metabolism and Potential for Drug-Drug Interactions

[redacted]

4.5.1. Transporters: Interactions

[redacted]

Kindolor also is an inhibitor of OAT1, OAT3, and MATE2-K renal transporters. At therapeutic concentrations, kindolor would not effectively inhibit OAT3, and thus, is not of major concern for DDI. On the other hand, since kindolor is a high affinity inhibitor of OAT1, kindolor could inhibit transport of OAT1 substrates at therapeutic concentrations, such as adefovir, zidovudine, ciprofloxacin and numerous NSAIDs, statins, and antibiotics. Since DDI potential exists at the OAT1 transporter, medications that are OAT1 substrates will be excluded in Phase 1a trials. Of note, however, circulating levels of uric acid, an endogenous substrate of OAT1 (Rizwan-2007), were not elevated following 14-day repeated administration of high doses of kindolor tosylate in rat and minipig, suggesting inhibition of OAT1 *in vivo* may be low. Kindolor can also be considered a high affinity inhibitor of MATE2-K. This transporter is located on the apical side of the proximal tubule cell and is not likely exposed to kindolor. Additionally, circulating levels of creatinine, an endogenous substrate of MATE2-K (Tanihara-2007), were not elevated following 14-day repeated administration of high doses of kindolor tosylate in rat and minipig. Therefore, the DDI potential of kindolor at MATE2-K *in vivo* is predicted to be low.

Kindolor can be considered a high-affinity inhibitor of the OATP transporters (OATP1B1, OATP1B3, OATP2B1) and a substrate for OATP1B1. Kindolor interacts with PEPT1, although this transporter exhibits lower affinity for kindolor. Therefore, kindolor could interact *in vivo* with the numerous drugs that are substrates or inhibitors of the OATP liver transporters and/or OATP2B1, which is an uptake transporter in liver, intestine, placenta, heart, and skin (Kalliokoski-2009), as well as PEPT1. Such interactions would depend on affinity, capacity, and saturability of the uptake transporters. In Phase 1a trials, all medications will be excluded. The reason for such a decision is that the characteristics of the transporters on which attention has

been focused with regard to kindolor, are notably different among species (Chu-2013), and PK data from humans will allow proper focus on the relevant drug transporters. After completion of Phase 1 studies in healthy subjects, the sponsor plans to perform studies of likely concomitant medications that are known transporter substrates in the indicated patient population.

4.5.2. CYP450 Enzymes: Induction and Competition

Kindolor moderately increased the expression (mRNA) of CYP2B6 and CYP2C9; however, in the case of Cyp2C9, enzyme activity was decreased after exposure to kindolor. In terms of CYP450 induction as a component of drug-drug interactions, CYP2B6 metabolizes various drugs, including artemisinin, bupropion, cyclophosphamide, efavirenz, ketamine, and methadone (Mo-2009). CYP2C9 has a broad substrate specificity, including angiotensin receptor blockers, warfarin, NSAIDs and sulfonylureas (Van Booven-2010). Whether modest increases in mRNA, in one case not reflected by increases in enzyme activity, would result in increased metabolism of other drugs, would best be considered in initial studies with humans. It should be noted that the abundance of DCUKA-OH was not increased in repeat dosing studies with kindolor, suggesting that induction of CYP2C9 did not affect *in vivo* metabolism.

[redacted]

4.6. Kindolor Tosylate Pharmacokinetics

[redacted]

Recovery of kindolor and its metabolites in the urine and feces of the preclinical species, in combination with the PK profiles of kindolor and its metabolites in plasma, and the known activity of kindolor as a BCRP transporter substrate, suggest that kindolor is excreted predominantly by the biliary system and the feces. Kindolor did not appear to be significantly excreted via the renal system. Based on the circulating concentrations of DCUKA-OH, DCUKA-gluc, and DCUKA-OH-gluc and the percent of these metabolites recovered in the excreta, kindolor does not appear to be extensively metabolized *in vivo* via Phase 1 and Phase 2 metabolic pathways.

4.7. Nonclinical Safety

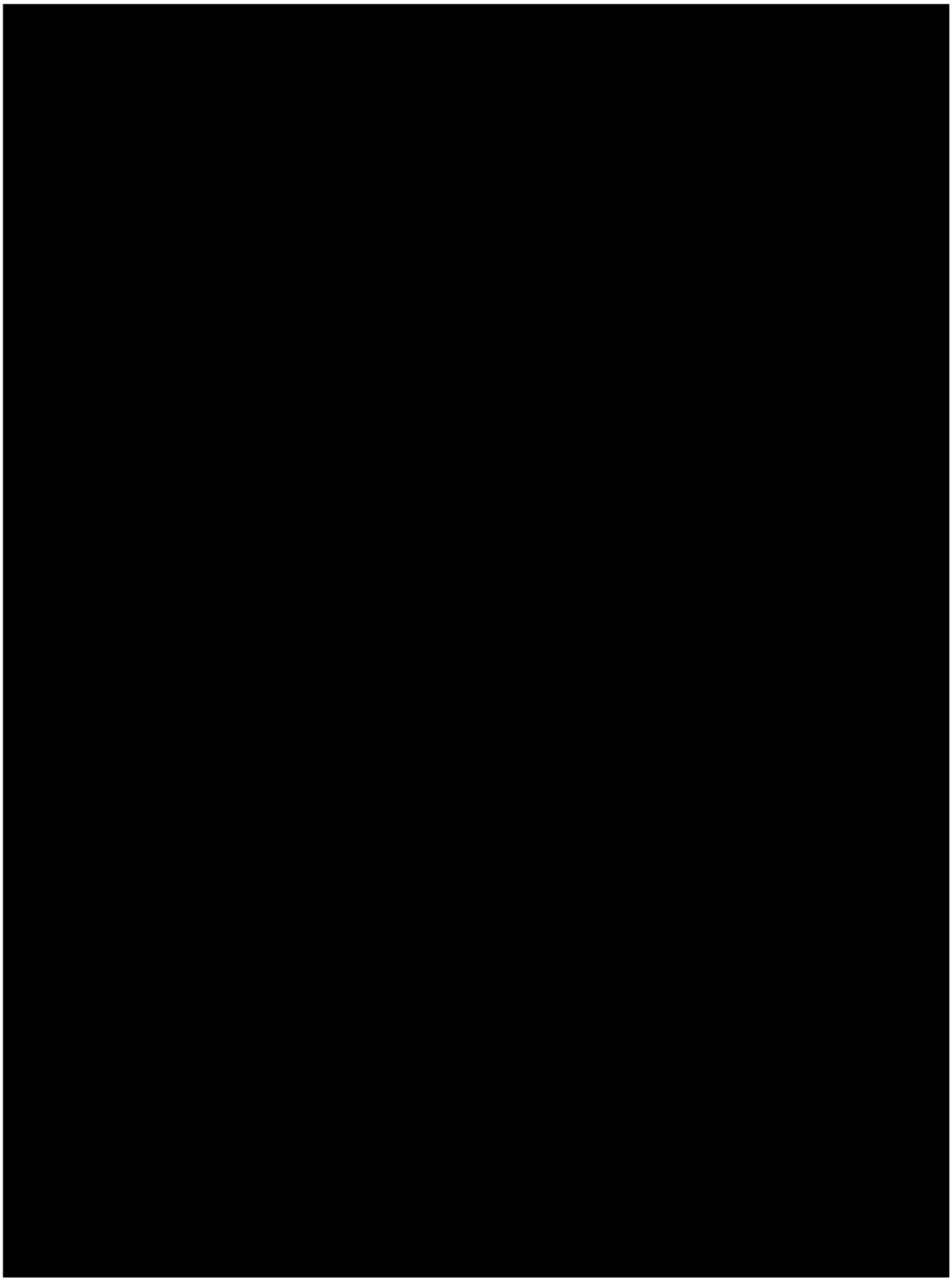
4.7.1. Safety Pharmacology Studies

[redacted]

4.7.2. Toxicology Studies

4.7.2.1. Pathology Findings

[redacted]



[redacted]

4.7.3. Genotoxicity Studies

[redacted]

4.7.4. Discussion of Study Design

This first-in-humans study was designed based on the data generated from toxicology and toxicokinetic studies in rats and minipigs. The starting dose and dose escalation scheme are discussed in the next section (Section 4.8). The blood collection scheme for determination of PK parameters was based on the t_{max} and $t_{½}$ to ensure that sufficient samples were collected soon after dosing to determine the C_{max} and t_{max} as accurately as possible while collecting samples to 48 hours after dosing to determine the terminal elimination rate constant (λ_z). Because of the potential for gastric toxicity found at higher relative doses in nonclinical species, a fecal occult blood test (FOBT), and questionnaires to assess changes in stool consistency and other GI symptoms (Appendix A and Appendix B). An endoscopy will be performed if signs gastric inflammation or erosion are reported or found on laboratory evaluation. Full blood chemistry, hematology, amylase, lipase and coagulation tests along with medical urinalysis will be performed. Vital signs will be closely monitored after dosing, and subjects will be confined to the Phase 1 unit from the start of dosing for 48 hours (more than 5 half-lives of kindolor in rats or minipigs), and then will return for final safety assessments at 7 ± 2 days after clinic discharge. Given the potential for gastric toxicity, an enteric coated tablet was developed for human use.

4.8. Rationale for Selection of Doses for this Study

For this first-in-humans study, the FDA "Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" was followed by considering the human equivalent dose (HED) in two relevant species (rats and minipigs) evaluated in the nonclinical toxicology studies as shown in Table 4. The basis for the starting dose is the HED in rats, as rats had the lowest HED at the NOAEL. Taking a conservative approach, instead of starting at $1/10^{th}$ the HED in the most sensitive species (rats), a starting dose in humans of 100 mg was selected which is 82-fold less than the rat HED. The highest dose to be tested in humans is 1800 mg. This dose is below the rat NOAEL at the same HED by 4.5-fold.

Table 3: Estimated Margins for Kindolor Tosylate Based on HED Relative to the Starting Human Dose

Species	Duration	Route	NOAEL Kindolor tosylate (mg/kg/day)	HED[a] Kindolor tosylate (mg/kg/day)	HED Kindolor tosylate (mg/day)[b]	Starting Dose in Humans Kindolor tosylate (mg)	FIH Starting Dose[c] Fold-lower relative to Rat HED
Rat	2 weeks	Oral	846	136	8160	100	82
Minipig	2 weeks	Oral	622	444	26,640	100	266

[a] The human equivalent dose (HED) was calculated by dividing the NOAEL by 6.2 for rats and 1.4 for micropigs and then multiplying by average body weight of 60 kg.
[b] Based on 60 kg human.
[c] Based on a proposed first-in-humans (FIH) starting dose of 100 mg and a proposed maximum dose of 1800 mg.

In the rat STZ model of PDN, 32.5 mg/kg and 40 mg/kg of kindolor (free base), equivalent to 45 mg/kg and 55 mg/kg kindolor tosylate, completely reversed tactile hyperalgesia. These doses produced plasma levels of 4.5-15.5 µM kindolor. The HED at these efficacious doses in rats are 7.2 mg/kg and 8.8 mg/kg of kindolor tosylate, respectively, which for a 60 kg adult are doses of 431 mg and 530 mg kindolor tosylate, respectively.

In a CFA inflammatory pain model, 34.5 mg/kg kindolor tosylate (equivalent to 25 mg/kg kindolor free base) completely reversed thermal hyperalgesia in the rat. The HED of kindolor tosylate is 5.5 mg/kg for the 34.5 mg/kg effective doses in the CFA rat models. This method provides a preliminary estimate of a potentially effective dose of kindolor tosylate in human (331 mg for a 60 kg human).

Based on the above animal models, the highest dose in humans (1800 mg) is predicted to be approximately 3.6- to 6-fold higher than the predicted efficacious dose.

Thus, the dosing scheme, shown in Table 5, brackets the potentially effective dose of 331 mg to 431 mg of kindolor tosylate for a 60 kg human while at the same time starting at a relatively low dose based on the toxicology profile in rats and minipigs.

Table 4: Kindolor Tosylate Dose Escalation Scheme

Cohort	Kindolor Tosylate Dose mg/kg[a]	Kindolor Tosylate Dose (mg)
1	1.7	100
2	5.0	300
3	15.0	900
4	45.0	1800

[a] Based on a 60 kg human.

4.9. Benefit/Risk Assessment/Protection Against Risks

Since this is a Phase 1 study, there are no benefits to the subjects. However, given the current opioid epidemic and the need for safer, more effective non-opioids to treat pain, there are significant benefits to society.

The risks of the study drug are not yet fully known in humans. The nonclinical safety profile of kindolor tosylate has been well characterized through the conduct of genetic toxicology, safety pharmacology, and acute and repeat dose (7-14 days) toxicology studies. Kindolor tosylate is not genotoxic and is not expected to have effects on the central nervous, respiratory, or cardiovascular systems in humans at clinically relevant doses.

The most notable adverse effect associated with kindolor tosylate was the result of local toxicity to the stomach. Repeated oral administration of kindolor tosylate resulted in adverse effects in the stomach in minipigs and to a much lesser extent, in rats. This was characterized initially by soft feces in the minipig. At the end of the dosing period, erosions and ulcerations were observed in the stomachs of rats and minipigs. However, doses that did not cause these effects were identified in both species after repeat dosing over 14-days. Thus, given that single doses, and an enteric coated formulation will be used in this study, the risk of GI toxicity should be low.

Increases in total bilirubin were observed in both rats and minipigs and may be related to the fact that kindolor is a high affinity inhibitor of OATP1B1 and OATP1B3 transporters. There were, however, no correlative histological observations or other clinical chemistry changes, and hepatic effects were reversible upon cessation of dosing. In minipigs only, an increase in renal tubular degeneration/regeneration was noted in both sexes at the two highest doses tested. This renal lesion, commonly observed in nonclinical safety studies, was reversible upon cessation of exposure and was considered non-adverse due to the minimal nature and lack of correlative clinical pathology suggestive of organ dysfunction. Additionally, no alterations in renal parameters (clinical chemistry or histology) were noted in the second minipig study at doses of kindolor tosylate up to 622 mg/kg/day (HED of 444 mg/kg/day).

To minimize risks to study subjects, an enteric coated tablet of kindolor tosylate has been developed that does not dissolve in solutions that mimic gastric fluid but does dissolve in solutions that mimic the intestinal environment that will be used in this first-in-humans study. The starting dose is conservatively 80-fold lower than the HED in the most sensitive nonclinical species (rats). Gastric toxicity will be specifically monitored in accordance with the plan in Section 11.1.5. There is an extensive array of clinical laboratory tests consistent with first-in-human studies. Although there is no evidence of cardiovascular toxicity in *in vitro* and *in vivo* studies, vital signs and ECG parameters will be closely monitored throughout the 5-half-life period after drug dosing.

Kindolor tosylate may have phototoxic potential that may appear as an exaggerated sunburn reaction (reddening and swelling) or in severe cases, vesicles, blisters and bullae may occur. In minipigs, the average elimination half-life of kindolor ranged 3.21 to 4.36 hours depending on the dose. Five half-lives, which approximates 99% elimination of circulating levels is 22 hours for kindolor with a 4.36-hour half-life. Therefore, subjects will not be exposed to sunlight while in the Phase 1 unit and will be cautioned to limit exposure to direct sunlight after release and to apply a sun protectant lotion to exposed areas of the skin after release for at least another 24 hours.

Safety data will be monitored by the principal investigator (PI), other study physicians, the medical monitor, and clinical monitors throughout all aspects of the study. The DSMB will review the safety data (AEs, vital signs, ECG, and clinical laboratory data) as each cohort completes the final 7-day safety visit and will approve escalation to the next dose before any additional subject cohorts are enrolled.

The main procedure risks are related to the multiple blood draws (total volume of blood to be collected for PK and other clinical laboratory tests is not expected to exceed 168 mL). If an endoscopy is performed, its most severe risks include infection, perforation of the esophagus or stomach, and bleeding.

There is a minor risk of loss of confidentiality; however, controls are in place to maintain protected health information securely both in paper copy and electronically. All clinical specimens will be deidentified prior to storage.

5. STUDY DESIGN

This is a Phase 1a, randomized, double-blind, single ascending dose study designed to assess the safety, tolerability, and PK of kindolor tosylate. Healthy male and female adults will be screened for eligibility by medical history, physical examination including height and body weight, vital signs, 12-lead electrocardiogram (ECG), clinical laboratory tests (chemistry, hematology, amylase, lipase and coagulation tests, medical urinalysis, and infectious disease screen), urine drug screen for drugs of abuse, fecal occult blood tests (FOBT), and medication use. Females will have a pregnancy test.

Using a dose escalating design, eligible subjects will receive randomly assigned oral tablets of kindolor tosylate (100 mg and 300 mg strengths) or identically matched Placebo tablets in 4 cohorts of 8 subjects (6 kindolor tosylate and 2 placebo in each cohort). A sentinel cohort of 2 subjects (1 active and 1 placebo) will be dosed and closely monitored for at least 24 hours prior to dosing the remaining 6 subjects in each successive cohort. Ascending doses of kindolor tosylate include 100 mg (1 x 100 mg tablet), 300 mg (1 x 300 mg tablet), 900 mg (3 x 300 mg tablet), and 1800 mg (6 x 300 mg tablet). The safety data for each completed cohort will be reviewed by the UCSD Clinical and Translational Research Data and Safety Monitoring Board (DSMB) that will recommend continuation to the next cohort or stopping the study due to safety concerns.

Eligible subjects will undergo intake procedures at the UCSD Clinical and Translational Research Institute Phase I unit on Study Day -1 (the day before starting dosing) and will complete final screening and baseline evaluations. On Study Day 1, subjects will receive the study drug after an overnight fast (about 8 hours) with no food allowed until 4 hours after dosing. Study drug tablets will be administered with 240 mL of water. Water will be allowed anytime except for one hour before and after dosing. Subjects will remain in the unit for at least an additional 48-hours for safety assessments and blood collections to determine plasma levels of kindolor. Pre-dose assessments will be conducted prior to administration of study drug on Study Day 1. Blood for PK analysis will be collected ~ 15 minutes prior to dosing, then at 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, and 48 hours after dosing. Safety will be assessed by collecting adverse events (AEs), vital signs, physical examination, ECG, FOBT, Stool Consistency Questionnaire, GI Signs and Symptoms Checklist, urine output (24 hours) and clinical laboratory tests (amylase, lipase, chemistry, hematology, coagulation tests, pregnancy tests, and urinalysis). AEs will be assessed daily after the start of dosing, with closer evaluations in the 4-hour period after the start of dosing. Sitting (3 minutes) vital signs will be taken during screening, at clinic check in, pre-dose, then at 15, 30, 60 minutes and 2, 4, 6, 12, 24, and 48 hours post dose. A 12-lead ECG will be obtained prior to dosing, then at 2, 6, 12, 24, and 48 hours post dose. When vital signs or ECG are scheduled at the same time as a PK blood draw, these assessments will be performed before drawing any blood. The FOBT will be performed at screening, clinic intake on Day -1, pre-discharge on Day 3, and at follow-up on Day 7. Subjects will return for a final follow-up visit 7 ± 2 days after discharge for a final safety assessment including ECG, vital signs, AEs, FOBT Stool Consistency Questionnaire, GI Symptoms Checklist, and clinical laboratory tests. Males will be contacted 90 days and females 28 days after study drug administration to verify continued contraceptive use and having not donated sperm for males and have not breast fed a baby or donated ova for females during this period. The study schedule of visits and assessments is shown in Table 6.

Table 5: Schedule of Visits and Assessments for Each Cohort

	Outpatient	Inpatient				Outpatient		Early Termination
Activity	**Screening**	**Clinic Intake**	**Treatment**	**Follow-up**	**Clinic Discharge**	**Follow-up**	**Telephone Contact[q]**	
Study Day	**-30 to -2**	**-1**	**1**	**2**	**3**	**7±2**		
Informed Consent	X							
Demographics	X							
Medical/Surgical History	X	update						
Physical Examination	X	update			X			X
Height/Weight	X	Weight only				Weight only		Weight only
12-Lead ECG[a]	X		X	X	X	X		X
Vital Signs[b]	X	X	X[c]	X	X	X		X
Serum amylase	X	X			X	X		X
Serum lipase	X	X			X	X		X
Clinical Chemistry[d]	X	X			X	X		X
Hematology[e]	X	X			X	X		X
Coagulation[f]	X	X			X	X		X
Urinalysis[g]	X	X			X	X		X
Monitor urine output[h]			X	X	X			
Infectious Diseases[i]	X							
SARS-CoV-2 Antigen Test[j]	X							

	Outpatient	Inpatient				Outpatient		Early Termination
Activity	**Screening**	**Clinic Intake**	**Treatment**	**Follow-up**	**Clinic Discharge**	**Follow-up**	**Telephone Contact[q]**	
Study Day	**-30 to -2**	**-1**	**1**	**2**	**3**	**7±2**		
Pregnancy Test[k]	X	X				X		X
Birth control methods	X	update			update		update	
Sperm, ova, donation and breast feeding check		X				X	X	
FOBT	X	X			X	X		
Urine Alcohol & Drug Screen[l]	X	X						
Prior and Concomitant medications[m]	X	X	X	X	X	X		X
Eligibility Checklist	X	Final check						
Genetics Tests[n]		X						
Study Drug Administration			X					
Blood Samples for PK[o]			X	X	X			
Adverse Events[p]			X	X	X	X		X
Stool Consistency		X	X	X	X	X		X
Final Subject Disposition						X		X

[a] A 12-lead resting ECG will be obtained at Screening, Day 1 prior to dosing, at 2, 6, 12, 24, and 48 hours post dose, and early termination.
[b] Vital signs include sitting (3 minutes) blood pressure, and heart rate, and oral temperature, respiration rate, and pulse oximetry.
[c] Blood pressure. and heart rate, respiration rate, and pulse oximetry will be taken pre-dose, then at 15, 30, 60 minutes and 2, 4, 6, 12, 24, and 48 hours post dose. Temperature will be taken pre-dose, 24, and 48 hours post dose. All vital signs will be taken at Day 3 before clinic discharge and Day 7.

[d] Chemistry tests include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, direct bilirubin, total bilirubin, alkaline phosphatase, creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), sodium, potassium, chloride, calcium, inorganic phosphorus, bicarbonate, uric acid, total cholesterol, total protein, glucose, and triglycerides. Details are provided in Section 11.1.5.

[c] Hematology tests include hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, absolute counts for neutrophils, lymphocytes, monocytes, basophils, eosinophils, and platelets.

[f] Coagulation tests include prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and international normalized ratio (INR).

[g] Urinalysis tests include specific gravity, pH, bilirubin, urobilinogen, ketones, protein, blood, glucose, nitrites, and leukocyte esterase. A microscopic evaluation will be performed if blood or leukocyte esterase are detected.

[h] Urine output will be monitored by collection of urine for two 24 hr periods, starting with the morning void on Day 1 then again starting over with the morning void on Day 2 to 24 hours later.

[i] Hepatitis A virus immunoglobulin M (HAV-IgM), hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab), HIV antibodies (HIV Ab).

[j] Results must be available within 72 hours of clinic intake.

[k] A serum test for beta-human chorionic gonadotropin (β-hCG) will be performed on all women unless they are menopausal. For any post-menopausal females, a follicle stimulating hormone (FSH) test will be performed to confirm sterilization in lieu of a β-hCG test. If clinic intake is within 72 hours of a negative test, it does not need to be repeated at intake. At intake, a rapid test for β-hCG may be performed.

[l] The urine drug test panel includes amphetamines, barbiturates, benzodiazepines, buprenorphine, cocaine, fentanyl, MDMA, methadone, methamphetamine, morphine, opioids, oxycodone, phencyclidine, and THC. Recent alcohol use will be assessed via ethyl glucuronide urine test strip.

[m] Medication use in the two months prior to the start of screening and at any time during the study after signing informed consent will be recorded.

[n] CYP2C9 polymorphisms

[o] Blood for PK will be collected ~ 15 minutes prior to dosing, then at 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, and 48 hours after dosing.

[p] GI AEs will be assessed specifically using a GI Signs and Symptoms Checklist, Stool Consistency Questionnaire, and endoscopy if indicated along with other laboratory tests as scheduled.

[q] Telephone contact for males at 90 days and for females at 28 days after dosing.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of the study is to determine the safety and MTD of kindolor tosylate in healthy volunteers.

6.2. Secondary Objective

The secondary objective of the study is to determine the PK of kindolor tosylate by quantitating kindolor levels in plasma across a range of doses in healthy volunteers.

7. STUDY INTERVENTIONS

7.1. Investigational Products

Investigational products will be provided by Lohocla Research Corporation. Kindolor tosylate will be supplied as a tablet in 100 mg and 300 mg dosage strengths in opaque plastic bottles. The number of tablets to be dispensed based on the randomized treatment groups is shown in Table 7. Placebo tablets of identical appearance to the two kindolor tosylate dosage strengths will be dispensed in the same numbers of tablets for that cohort. Tablets will be administered with approximately 240 mL of water. Dosing will be after an approximate 8-hour fast, 4 hours before any food will be given, and 1 hour before water will be given to quench thirst.

Table 6: Kindolor Tosylate Dosing Plan

Cohort	Kindolor Tosylate Total Dose (mg)	Tablet Size (mg)	Number of Tablets
1	100	100	1
2	300	300	1
3	900	300	3
4	1800	300	6

7.2. Investigational Product Labeling and Dispensing

A preprinted label will be on investigational product bottles with the following information: The study number, the words Kindolor Tosylate and the tablet strength in mg and number of tablets. The label will also have the storage conditions, and the words “Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use” and “Keep Out of Reach of Children”. Tablets of the appropriate strength for the randomized treatment assignment will be dispensed by an unblinded research pharmacist into a standard pharmacy plastic container. The label affixed to the container will include a place to record the subject ID number, dose strength (for placebo tablets this will be the equivalent mg of kindolor tosylate tablets), and date dispensed. The date and time that the dose was administered to the subject will be recorded.

7.3. Investigational Product Storage

Kindolor tosylate tablets must be stored at room temperature (within the range of 59°F to 86°F; 15°C to 30°C) protected from light in a secured area at the clinical site.

7.4. Investigational Product Accountability

The site principal investigator (PI) or designated study personnel will maintain a log of the receipt of all investigational products and record of dispensing of all investigational products to the subject. Investigational product for each subject will be inventoried and accounted for throughout the trial. The site PI or his/her staff will count the individual unused vials remaining at the end of the study and record the vial count on the appropriate drug accountability form.

7.5. Used/Unused Investigational Product Supplies

Unused investigational products will be retained at the clinical site until the end of the study. After final accountability has been performed, investigational products will be destroyed according to the site's standard operating procedures.

7.6. Concomitant Medications

Subjects will be excluded from the study if they are taking any over-the-counter and/or prescription medication, vitamins, and/or herbal supplements (including cannabis and cannabis-derived product, including cannabidiol (CBD)-containing products) on a regular basis or use of any of these within the 2 weeks or 5 half-lives of the respective medication prior to study drug administration.

Medications are permitted to treat adverse reactions occurring after dosing at the discretion of the PI. Subjects will be instructed to check with study staff before taking any new medications. Subjects will be informed that starting any new medication without consulting study staff could pose health risks.

8. STUDY PROCEDURES

8.1. Recruitment of Subjects

Subject recruitment methods will be based on the site's local population targeting men, women, and all racial/ethnic groups; however, standard tactics may be used (i.e., flyers, newspaper advertisements, internet sites, radio advertisements, and television advertisements). In addition, UCSD has a large database of healthy volunteers. The UCSD undergraduate campus is next to the Phase 1 unit and institutional review board (IRB) approved flyers will be posted on campus. Research Match will also be used to identify subjects. The screen failure rate is anticipated at about 20%. The local IRB will approve all advertising materials used for subject recruitment. Interested candidates responding to recruitment materials by telephone will be asked to complete a standardized telephone interview that includes questions about their health status, interest in participation, and availability for an inpatient clinical trial. Study staff will ask these questions without revealing the entry criteria for the study. Candidates who report information consistent with the entry criteria and appear to be available and interested in the study will meet with the investigator or designated investigational staff after the initial inquiry to start the informed consent and assessment process.

8.2. Informed Consent

At the first screening visit, candidates will meet with either the site PI or his/her designee and receive an explanation of the study purpose and requirements. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the study informed consent form approved by the IRB. Subjects will be given a copy of the signed informed consent form. All subjects who sign informed consent must be registered in the electronic data management system (EDMS) as enrolled in the study. The EDMS will assign the subject a unique subject ID number that will be used on all of the data collection forms and electronic system entries.

8.3. Selection and Withdrawal of Subjects

8.3.1. Inclusion Criteria

Subjects must meet each one of the following inclusion criteria in order to be eligible for participation in the study:

1. Healthy male or female volunteer, ages 18-to-55 years, inclusive.
2. BMI must be between 18 and 32 kg/m^2 (inclusive) and weigh a minimum of 50 kg (110 lbs). BMI is calculated as weight in kg divided by the square of height measured in meters.
3. A condition of general good health, based upon the results of a medical history, physical examination, vital signs, laboratory profile, and a 12-lead electrocardiogram (ECG).
4. If female, be postmenopausal (at least 2 years prior to dosing), surgically sterile (6 months post tubal ligation), or agree to use an acceptable form of birth control from screening until 28 days after dosing. Subjects who claim postmenopausal status will have

status confirmed with a follicle-stimulating hormone (FSH) test. Acceptable forms of birth control for females include the following:

- Vasectomized partner (at least 6 months prior to dosing)
- Surgical sterilization (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) at least 6 months prior to dosing
- Non-surgical permanent sterilization (eg, Essure procedure) at least 3 months prior to dosing
- Double barrier (diaphragm with spermicide; condoms with spermicide)
- Nonhormonal intrauterine device
- Abstinence (must agree to use a double barrier method if they become sexually active during the study)

5. If male, agree to use an acceptable method of birth control during the study and 90 days following dosing. Acceptable forms of birth control for males include the following:
   - Vasectomy (at least 6 months before dosing)
   - Partner is surgically sterilized (see methods above for females)
   - Partner uses oral, injectable, or implantable hormonal contraceptives or intrauterine device (IUD)
   - Double barrier (partner uses diaphragm with spermicide; condoms with spermicide)
   - Abstinence (subject must agree to use a double barrier method if subject becomes sexually active during the study)
6. If female, agree to not breastfeed or donate ova from the time of consenting to the study and for 28 days after dosing the study drug.
7. If male, agree to not donate sperm from the time of consenting to the study and for 90 days after dosing the study drug.
8. Be able to verbalize an understanding of the consent form, able to provide written informed consent, verbalize willingness to complete study procedures, able to understand written and oral instructions in English.
9. Complete all assessments required at screening and baseline and be available to stay in the Phase I unit for a period of approximately 4 days and 3 nights and return for a follow-up visit.
10. Provide contact information of someone, such as a family member, spouse, or significant other, who may be able to contact the subject in case of a missed clinic appointment.
11. Be someone who in the opinion of the investigator would be expected to complete the study protocol.

8.3.2. Exclusion Criteria

Subjects will not be eligible to participate in this study if any one of the following exclusion criteria is met:

1. History of significant sensitivity to any drug.
2. Requirement for any over-the-counter and/or prescription medication, vitamins and/or herbal supplements (including cannabis and cannabis derived products, including CBD-containing products) on a regular basis or use of any of the above within 14-day period prior to clinical intake and agree to not use any of these medications for the duration of the study.
3. More than moderate alcohol consumption in the past 8 weeks. Moderate alcohol consumption is defined as limiting intake to 2 drinks or less in a day for men and 1 drink or less per day for women. Examples of one drink include: Beer: 12 fluid ounces (355 milliliters); Wine: 5 fluid ounces (148 milliliters); Distilled spirits (80 proof): 1.5 fluid ounces (44 milliliters).
4. Has a clinically significant laboratory test that is out of range of normal limits. An out of range of normal limit laboratory value is clinically significant if associated with one of the following: a) clinical diagnosis; b) systemic signs and symptoms; c) physical exam finding; d) more than 20% above the upper or below the lower limit of normal (for CPK, 1.5 times the upper limit of normal and based on the subject's medical history).
5. Have a urine toxicology screen positive during screening or baseline for any of the following substances:
    a. ethylglucuronide (alcohol metabolite),
    b. amphetamines,
    c. barbiturates,
    d. benzodiazepines,
    e. buprenorphine,
    f. cocaine,
    g. fentanyl,
    h. methylenedioxymethamphetamine (MDMA),
    i. methadone,
    j. methamphetamines,
    k. morphine,
    l. opioids,
    m. oxycodone,
    n. phencyclidine and/or
    o. tetrahydrocannabinol (THC)
6. If female, positive pregnancy test or nursing.
7. Positive test result for hepatitis A virus immunoglobulin M (HAV-IgM), hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (HCV Ab) or HIV antibodies (HIV Ab). Negative HIV status will be confirmed at Screening, and the results will be maintained confidentially by the study site.

8. Positive SARS-CoV-2 antigen test prior to 72 hours of clinic intake.
9. History of any clinically significant cardiac, respiratory , renal, hepatic, gastrointestinal, hematologic, endocrine, dermatological, metabolic, neurological (nerve injury) or psychiatric disease or disorder, or any uncontrolled medical illness.
10. History of gastroesophageal reflux disease, gastrointestinal ulcers, gastrointestinal bleeding, inflammatory bowel disease or gastroesophageal surgery.
11. Use of any known strong CYP3A4 inhibitors (e.g., ketoconazole) or dual CYP3A4 and 2C9 inhibitor (eg. Fluconazole), or dual CYP3A4 and 2C9 inducer (eg. Rifampin), or use of any monoamine oxidase inhibitors (MAOIs) within 1 month prior to study drug administration.
12. Receipt of any drug by injection within 30 days prior to study drug administration.
13. History of head trauma with loss of consciousness, history of epilepsy, seizures or convulsions, including febrile, alcohol, or drug withdrawal seizures.
14. A clinically notable vital sign abnormality including a history of syncopal or near syncopal events following abrupt change in posture.
15. Have any of the following at screening or baseline:
    - Blood pressure: systolic >140 mmHg, diastolic >90 mmHg at Screening or Day -1.
    - Heart rate: >100 beats/minute at screening or Day -1
16. History of cardiovascular abnormality, including left ventricular dysfunction, sick sinus syndrome, family history of long-QT syndrome, or unexplained sudden deaths in their family.
17. Has a clinically significant abnormal ECG or an ECG with a QTc interval corrected for heart rate using the Fridericia formula (QTcF) > 430 msec.
18. History of gastric surgery, vagotomy, bowel resection, or any surgical procedure that might interfere with gastrointestinal motility, pH, or absorption.
19. Has an estimated creatinine clearance (CrCl) outside of normal range.
20. Donation or loss of 550 mL or more blood volume (including plasmapheresis) or receipt of a transfusion of any blood product within 8 weeks prior to study drug administration.
21. Receipt of any investigational product within 6 weeks prior to study drug administration.
22. Consumption of alcohol within the 1-day period prior to study drug administration.
23. Consumption of grapefruit or grapefruit products from 3 days prior to study drug administration to study drug administration.
24. Use of tobacco or nicotine-containing products within the 6-month period preceding study drug administration.
25. Current enrollment in another clinical study.
26. Previous enrollment in this study.

27. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to receive kindolor tosylate.

8.4. Eligibility Screening

After the subject signs informed consent, screening may begin. During the first screening visit, subjects will undergo the following assessments:

- Demographics
- Medical/Surgical History
- Physical Examination
- Height/Weight
- 12-Lead ECG
- Vital Signs
- Clinical laboratory tests including chemistry, hematology, amylase, lipase, coagulation, urinalysis, infectious diseases, Urine Drug/Alcohol Screen, and Pregnancy Test
- SARS-Cov-2 Antigen Test (must be obtained within 72 hours of clinic intake)
- Birth control methods for men and women
- Prior and Concomitant medications

Assessments can be performed in any order except that it is recommended to take vital signs prior to blood draws. If any of these assessments reveal that the subject is not eligible for the study, screening can be immediately terminated, and no further data be collected. Clinical laboratory tests may be repeated at the discretion of the investigator if the first assessment yields values outside normal laboratory limits.

After all screening assessments are completed and if the subject is still considered eligible, they will be instructed not to take any new medications, or they may not be able to participate in the study and will be instructed to continue to use an appropriate method of birth control. The subject will be provided with Hemoccult blood test supplies for FOBT and with instructions to collect a stool specimen at home and to mail back the sample to the clinic for microscopy. Females should not take the test during their period as menstrual blood may end up in the sample leading to a false positive. The instructions will include the following dietary restrictions:

Starting 3 days before you begin collecting your stool samples, avoid:

- Red meat, such as beef, lamb, or liver
- Raw fruits and vegetables
- Vitamin C, such as fruit juices with vitamin C and vitamin C supplements in doses higher than 250 mg per day
- Antacids (medications to relieve heartburn or stomach pain, such as Tums®)
- Medications to stop diarrhea (loose or watery bowel movements)

- Iron supplements

8.5. Day -1 Baseline and Final Eligibility Assessments Evaluated at Clinic Intake

If the subject is eligible after performing all the initial screening assessments, s/he will be scheduled to start the study and will come to the clinic for a final eligibility check and complete the baseline assessments on Day -1. A sentinel cohort of 2 subjects (1 assigned to receive kindolor tosylate and 1 assigned to receive placebo) will be dosed and closely monitored for at least 24 hours after receiving drug for AEs, prior to clinic intake and dosing the remaining 6 subjects in each successive cohort. No more than 2 subjects will be dosed on a single day of these 6 subjects.

For final eligibility determination, the following will be assessed at clinic intake on Day -1:

- Medical/Surgical History update
- Physical Examination update
- Weight
- Vital Signs
- Birth control methods for men and women update
- Pregnancy test (women only) (must be obtained within 72 hours prior to dosing)
- Prior and Concomitant medications

For baseline, the following will be performed:

- Clinical laboratory tests including chemistry, amylase, lipase, hematology, coagulation, urinalysis, and urine drug/alcohol screen
- FOBT

Blood for DNA genomics will be collected if the subject is still eligible.

The screening period will not be extended. If the investigator determines that the subject could be a viable participant who could not for extenuating circumstances complete the screening period in 30-days, the subject can be re-screened by completing all of the screening assessments again. In this case, the subject will be assigned a new subject number.

8.6. Day 1 Dosing, and Pre- and Post-Dosing Assessments

Urine output will be monitored over two 24-hour periods starting with the morning void on Day 1 and finishing through Day 3 prior to the morning void. The start time and end time of these two collection periods will be recorded and the amount collected during these 24-hour periods will also be recorded. After the subject is determined to be eligible and baseline assessments are completed, the subject will be randomized to treatment.

The dose of the assigned investigational product will be taken orally with approximately 240 mL of water after an approximate 8-hour fast and 4 hours before any food or beverage other than water to quench thirst under the supervision of study staff. Water can be given 1 hour after dosing.

Blood for PK will be collected ~ 15 minutes prior to dosing, then at 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, and 48 hours after dosing. Blood pressure and heart rate will be taken pre-dose, then 15, 30, 60 minutes and 2, 4, 6, 12, 24, and 48 hours post dose. If vital signs are more than 25% outside baseline levels, measurements will be repeated until they normalize.

A 12-lead resting ECG will be obtained prior to dosing, at 2, 6, 12, 24, and 48 hours post dose. A nurse will always stay with the subject for 4 hours after the dose and observe the subject for AEs and ask the subjects an open-ended question about how they are feeling and ask specifically about any epigastric discomfort.

8.6.1. Confinement

Subjects will be confined to the study site and supervised over a 4-day period starting on Study Day -1. Confinement will conclude after the scheduled study procedures are completed on Study Day 3. Strenuous activity during confinement will not be permitted.

8.6.2. Meals, Dietary Requirements, and Other Restrictions

Subjects will receive a standardized diet, providing approximately 30% of the daily calories from fat, for all meals during confinement. Subjects will start fasting on Study Day -1 after the evening meal and should be fasting for about 8 hours with no food allowed until 4 hours after dosing on Day 1. Starting with lunch on Study Day 1 until after the 24-hour blood collection on Study Day 3, the subjects will consume only the scheduled meals provided in the study and water to quench thirst. The subjects will abstain from all other food and beverage.

On the morning of dosing, non-caffeinated and nondairy liquids are permitted prior to dosing, but food is prohibited. No food or beverage, except for water to quench thirst, will be allowed on Study Day 1 from study drug dosing until after the collection of the 4-hour blood sample.

On Study Day 1 subjects will be served lunch following the 4-hour blood collection. The composition (protein, fat, carbohydrate, and total calories) of this meal will be determined by a dietician and a record will be kept with the source documents. The sequence of starting meals on the dosing days will be maintained such that the time intervals between dosing and meals are essentially the same for all subjects in each period. Subjects may not consume:

- Red meat, such as beef, lamb, or liver or raw fruits and vegetables,
- Alcohol within the 2-day period prior to any study drug administration,
- Grapefruit or grapefruit products during the study, or
- Caffeine during confinement.

Kindolor shows phototoxic potential, therefore, subjects will not be exposed to sunlight while in the Phase 1 unit and will be cautioned to limit exposure to direct sunlight after release and to apply a sun protectant lotion to exposed areas of the skin after release for at least another 24 hours.

8.7. Measures Taken to Minimize/Avoid Bias

8.7.1. Randomization

Each of the first two subjects in each cohort will be randomized to receive kindolor tosylate or Placebo. The remaining 6 subjects in the cohort will be randomized in a 5:1 ratio to receive kindolor tosylate or Placebo. As much as possible, groups will be balanced with respect to gender during randomization.

8.7.2. Blinding

Only the research pharmacist will know the identity of the investigational product. The research pharmacist will keep the randomized assignment of subjects in a secure location. All other study staff will be blinded to treatment given. The site investigator or designated, approved study physician will make the decision to un-blind the identity of the investigational product if the study blind needs to be broken to make medical decisions regarding subject treatment. If it is determined that unblinding is necessary to assess AEs or SAEs for expedited reporting, the sponsor may decide to request unblinding of a subject.

8.8. Assessments on Days 2, 3 and at the Final Outpatient Visit

Assessments (vital signs, laboratory tests, ECG, Stool Consistency Questionnaire, GI Signs and Symptoms Checklist, and AEs) on Study Days 2 and 3 will be evaluated in accordance with Table 6. A final clinic visit will occur 7 ± 2 days after the dosing day and will also be in accordance with Table 6.

8.9. Final Telephone Contact

Males will be contacted at Day 90 (+ 1 week) to verify continued use of contraceptives and to have not donated sperm during this period. Females will be contacted at Day 28 (+ 1 week) to verify continued use of contraceptives and to have not donated ova or started breastfeeding during this period.

8.10. Early Termination Visit

If the subject requests to withdraw from the study early, early termination assessments will be scheduled if the subject agrees, and the assessments in Table 6 will be performed.

8.11. Emergency Preparedness

The Clinical and Translational Research Institute at UCSD is an 18,000 sq. ft. research clinic with over 20 clinic staff, research coordinators, and a Phase I unit. The Phase I unit is fully staffed by Advanced Cardiac Life Support certified nurses. The unit has all emergency equipment available in the event of a serious drug reaction. The facility has a 911 protocol with Emergency Medical Service available within 5 minutes for transport of the subject to the University of California Health System Emergency Room located across the street (door to door is less than 50 yards).

8.12. Duration of Subject Participation

Each subject will participate in the study for up to approximately 58 days for females and 120 days for males, including up to 30 days for screening, 4 days and 3 nights residing in the Phase 1 unit, with one follow-up visit 7 ± 2 days after discharge from the Phase 1 unit and a telephone call check at 28 days after dosing for females and 90 days after dosing for males for a verification contraceptive practices, and conformance with agreement not to donate ova, breastfeed, or donate sperm during this period.

8.13. Subject and Study Discontinuation and Stopping Criteria

8.13.1. Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including the occurrence of an AE or noncompliance with the protocol. Subjects who withdraw from the study will not be replaced unless it is mutually agreed upon, in writing, between the investigator and the sponsor.

Some specific considerations for replacement of subjects include:

1. If a subject is considered eligible for the study but does not receive any investigational product, another subject will be enrolled to ensure that each cohort has the target number of subjects.
2. If a subject is randomized to the active group but withdraws from the study before the Day 3 clinic release procedures are performed, then a replacement subject may be considered.
3. If a subject for some reason is missing safety measures such as clinical laboratory assessments, vital signs, or FOBT.
4. If a subject for some reason is missing blood samples for PK measurements such that PK cannot be determined.

If a subject withdraws or is discontinued from the study, the reason(s) for the discontinuation from the study will be recorded and a physical examination, body weight, vital signs measurement, ECG, laboratory analyses, Stool Consistency Questionnaire, GI Symptoms Checklist, and AEs will be performed as soon as possible after discontinuation from the study. Additional blood samples for drug measurement may be collected at the time of discontinuation from subjects who are discontinued due to AEs; the clock time, and date the sample was taken will be recorded.

If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or AE is achieved.

8.13.2. Dose Continuation, Dose Escalation and Study Stopping Criteria

Continuation of dosing within a cohort, or dose escalation to sequential cohorts will stop when either:

a) The highest dose is reached or,

b) Clinical/laboratory/AE findings meet any of the following stopping criteria:

i. Two or more subjects on active medication have clinical laboratory values meeting the criteria of moderate (Grade 2) intensity

ii. Two or more subjects on active medication experience moderate AEs of the same type (within the same MedDRA SOC)

iii. One or more subjects on active medication experiences any clinical laboratory value meeting the criteria of severe (Grade 3 or 4) intensity or an AE is determined to be severe in intensity

iiii. Any subject has a positive FOBT

c) The mean kindolor systemic exposure levels exceed AUC(Tlast)=87,550 ng.h/mL or Cmax >13,490 ng/mL in a single subject in a cohort.

d) The DSMB recommends stopping escalation after review of all the data from each cohort.

The maximum tolerated dose (MTD) will be considered the highest dose where no active medication subjects meet the study stopping criteria.

8.14. Study Termination Criteria

The sponsor may terminate this study prematurely, either in its entirety or at any site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to Lohocla Research Corporation in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. The FDA may stop the study at any time as well. If the FDA notifies the sponsor to stop the study, then the sponsor will notify the site of this action.

9. STUDY ENDPOINTS

9.1. Safety Endpoints

Safety endpoints include:

- AEs
- Stool Consistency Questionnaire indicative of a GI AE
- GI Signs and Symptoms Checklist indicative of a GI AE
- Clinical laboratory data
- ECG results
- FOBT results
- Vital signs
- Rate of urine output (24 hrs)

9.2. PK Endpoints

PK endpoints include:

AUC_t: Area under the plasma concentration-time curve from time 0 to the time (t) of last quantifiable concentration (C_t) calculated by the log-linear trapezoidal rule.

AUC_∞: Area under the plasma concentration-time curve from time 0 extrapolated to infinity. The terminal area from C_t to infinity was calculated by using the approximation as C_t/λ_z thus $AUC_\infty = AUC_t + C_t/\lambda_z$.

C_{max}: The maximum observed plasma concentration.

t_{max}: The observed time to reach maximum plasma concentration.

λ_z: The terminal-phase exponential rate constant as calculated from the negative slope of the regression line for the terminal linear portion of the LN transformed plasma concentration versus time curve.

$t_{½}$: The apparent terminal exponential half-life, calculated as $\ln(2)/\lambda_z$.

10. SAFETY MONITORING PLAN

Safety monitoring will be conducted throughout the study; therefore, safety concerns will be identified by continuous review of the data by the PI, clinic staff, clinical monitor, medical monitor, and the sponsor.

Study Safety Management: The IRB, Medical Monitor, PI, clinical monitors, and Lohocla Research Corporation will review any safety concerns throughout the trial. In addition, the UCSD DSMB will participate in this study. The roles of these individuals/committee are described below.

Medical Monitor: A Medical Monitor will be appointed by the sponsor for the study. The Medical Monitor will be available for making recommendations to the investigator and the sponsor on the severity of any SAEs, and the relatedness to the study interventions, and if laboratory excursions or other AEs meet the criteria for stopping escalation or stopping the study. The Medical Monitor will also be responsible for tracking and assessing trends in the AEs reported.

Clinical Monitors: All investigators will allow representatives of the contract research organization (Fast-Track Drugs and Biologics, LLC) to periodically monitor, at mutually convenient times during and after the study, all study data. These monitoring visits provide the clinical monitors and the sponsor with the opportunity to evaluate the progress of the study and to obtain information about potential problems. The monitors will assure that submitted data are accurate and in agreement with any paper source documentation used, verify that investigational products are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by Good Clinical Practices (GCP) guidelines are appropriately filed.

Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and GCP guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

Routine monitoring visits by the clinical monitors and the sponsor will be scheduled at appropriate intervals but more frequently at the beginning of the study. A monitoring visit soon after the first two subjects have been treated is planned. At these visits, the monitors will verify that study procedures are being conducted according to the protocol guidelines, monitor eCRFs against source documents, review AEs and SAEs, and perform drug accountability. At the end of the study, they will confirm that the site has the appropriate essential documents on file, advise on storage of study records, and inspect the return and destruction records for unused investigational products.

Sponsor Site Visits: All investigators will allow the sponsor full access to study records during site visits by the sponsor. Visits by the sponsor will be made at a mutually convenient time and will be scheduled in advance.

DSMB: The UCSD DSMB will meet prior to the start of the study, and after each cohort completes the study. As each cohort completes the study, a Fast-Track unblinded statistician will generate the appropriate tables and listings including PK data and a Fast-Track physician will

compile this safety data and prepare a safety report for presentation to the DSMB in accordance with the Operating Charter and planned analyses. *Ad hoc* meetings will be convened if SAEs occur that are considered at least possibly related to the investigational product or clinical, laboratory, or AE findings meet any of the stopping criteria (see section 8.12.2).

11. ASSESSMENT METHODS

All study assessments will be performed at the visits and time points outlined in the Schedule of Assessments (Table 6); the following sections outline the details and procedures associated with the assessments. All assessments will be recorded on a source document and transcribed into electronic case report forms (eCRFs).

11.1. Adverse Events and Serious Adverse Events

The investigator and study site staff are responsible for the detection, documentation, classification, reporting, and follow-up of events meeting the definition of an AE or SAE.

11.1.1. Adverse Event Definition

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and may not necessarily have a causal relationship with the administered treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory abnormality), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. Pre-existing conditions, diseases, or disorders are not considered AEs unless there is a change in severity or frequency.

11.1.2. Serious Adverse Events and Serious Unexpected Adverse Events Definition

An SAE is any untoward medical occurrence that meets one of the following:

- Results in death
- Is life-threatening (at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

A serious and unexpected AE is an SAE that is not identified in nature, intensity, or frequency in the risk information included in the Product Label for the drug.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the study subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

11.1.3. Methods/Timing for Assessing, Recording, and Analyzing Safety Endpoints

AEs will be assessed starting after the first administration of investigational product until the final follow-up visit. However, SAEs will be collected from the time of informed consent onward. General symptoms will be collected via an open-ended question: “How have you been feeling since your last visit or the last time we spoke?”

AEs will be documented in the source records and recorded on the eCRFs using accepted medical terms and/or the diagnoses that accurately characterize the event. When a diagnosis is

known, the AE term recorded on the eCRF will be the diagnosis rather than a constellation of symptoms. The investigator will assess all AEs for seriousness, relationship to investigational product, and severity. When an event has not resolved by study closure, it will be documented on the AE eCRF as "ongoing".

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study physicians until satisfactory resolution (the event either resolved or stabilized and is not expected to resolve in the near term). AEs must be reported up to 1 week after investigational product administration. At the final clinic visit, AEs will be recorded and followed to resolution only if they are serious, or if the study physician assesses them to be clinically significant.

11.1.4. Clinical Laboratory Abnormalities and Other Abnormal Assessments

Abnormal clinical laboratory findings (e.g., clinical chemistry) will be reported as an AE unless the value was outside normal laboratory limits at baseline and did not increase by a severity grade level at the follow-up assessment. Grade 2 or greater results for any other laboratory test will be considered clinically significant.

11.1.5. Gastrointestinal Adverse Events

Gastrointestinal (GI) AEs will be assessed as follows:

- Stool Consistency Questionnaire – subject completed questionnaire (Appendix A)
- GI Signs and Symptoms Checklist (Appendix B)
- FOBT
- Open ended questions about AEs that are indicative of gastritis
- Clinical laboratory tests (hematocrit, hemoglobin, blood urea nitrogen (BUN), creatinine, ALT, and AST)
- Endoscopy (if indicated)

A-subject completed Stool Consistency Questionnaire (Appendix A) that asks 4 questions about GI symptoms will be utilized to assess GI AEs. The responses to the questions are based on a 4-point scale with 0 being no symptom and 3 being a severe symptom. The development of a new symptom or worsening of an existing symptom will be reported as an AE.

In addition, if a subject reports of any of the signs and symptoms of gastritis or potential GI ulcer complications or has a laboratory test result indicative of blood loss as shown in the GI Signs and Symptoms Checklist (Appendix B), the study gastroenterologist sub-investigator will do a thorough evaluation of the event and perform an endoscopy if it is considered warranted. A signs and symptoms checklist will be reviewed each day starting with Day 1, and then on Days 2, 3, and 7. Presence or absence of each sign or symptom will be recorded and if appropriate, a severity assessment or clinical significance evaluation will be performed.

Clinically significant changes in hematocrit and hemoglobin are defined as decreases of at least 10 percentage points and 2 g/dL, respectively. Clinically significant changes in other clinical laboratory tests will be defined as blood **urea nitrogen** $\geq$ **40 mg/dL, creatinine** $\geq$ **1.8 mg/dL, ALT**

and AST ≥ 3 times the upper limit of normal. If there is evidence of gastric erosion, ulcer, or bleeding in any subject confirmed by endoscopy or FOBT, the study will be stopped.

11.1.6. Reporting Pregnancy

Pregnancy in a study subject within 30 days after study drug administration must be reported to the investigator within 1 working day of becoming aware of the pregnancy. Subjects who become pregnant during the screening period prior to study drug administration will not be randomized to receive treatment.

If the subject becomes pregnant during the study or up 30 days after study drug administration, then a Pregnancy Reporting Form must be completed and emailed to Fast-Track within 24 hours of becoming aware of the pregnancy. Pregnancies must be followed to conclusions and an updated Pregnancy Reporting Form should be emailed to Fast-Track within 24 hours of becoming aware of the conclusion of the pregnancy.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an spontaneous abortion, stillbirth, or congenital anomaly is considered an SAE and must be reported to the sponsor within 24 hours of the site becoming aware of the event.

11.1.7. Classification of Adverse Event Intensity and Relationship to Investigational Product

The severity of AEs or SAEs will be in accordance with the FDA's "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". For those not listed in the guidance, the following criteria will be used:

Mild:	An event that is usually transient, requiring no special treatment, and does not generally interfere with the subject's daily activities.
Moderate:	An event that interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject. The event is usually ameliorated with additional specific therapeutic intervention.
Severe:	An event that interrupts usual activities of daily living or significantly affects clinical status. The event poses a significant risk of harm to the subject and hospitalization may be required, and typically requires intensive therapeutic intervention.

However, as gastric AEs are a potential concern, and the toxicity grading scale stated above, does not cover some of the more serious gastric AEs such as gastritis and gastric ulcer, the Common Toxicity Criteria for Adverse Events Grading Scale (version 5.0) will be used for the severity of these AEs.

The investigator must assess relationship to the investigational product based on the following criteria:

Unrelated:	The subject did not receive the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is not reasonable, or there is another obvious cause of the AE/SAE.
Unlikely:	There is evidence of exposure to the investigational product but there is another more likely cause of the AE/SAE.
Possible:	There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, but the AE/SAE could have been due to another equally likely cause.
Probable:	There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, and the AE/SAE is more likely explained by the investigational product than by any other cause.
Definite	There is evidence of exposure to the investigational product, the temporal sequence of the AE/SAE onset relative to administration of the investigational product is reasonable, the AE/SAE is more likely explained by the investigational product than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the investigational product or investigational product class.

11.1.8. Outcomes and Actions Taken

All unresolved AEs will be followed for a minimum of 7 days (unless the AE is an ongoing pregnancy which must be followed to conclusion) after the subject's final study visit, unless the investigator's judgment dictates otherwise, the event has resolved or stabilized prior to the 7-day period, or the subject is lost to follow-up.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects that occur following the follow-up period.

For each recorded AE or SAE, the investigator must assess outcome at the time of last observation, as follows:

Fatal:	The subject died.
Resolved without Sequelae:	The AE or SAE has ended.
Resolved with Sequelae:	The AE or SAE has ended but changes are noted from baseline.
Unresolved – Ongoing:	The AE has not ended and is ongoing at the end of the reporting period (i.e., 7 days after the final Follow-up visit) and the investigator deems that further follow up is not medically required.
Unknown – Lost to Follow-up:	Lost to follow-up after repeated unsuccessful attempts to contact the subject.

If the AE was treated (medications or other physical measures), this will also be recorded.

11.1.9. Reporting Serious Adverse Events

11.1.9.1. 24-hour Reporting Requirements (Initial Report)

Any SAE, including death due to any cause, which occurs to any subject from the time of signing consent through the final follow-up visit whether or not related to the investigational product, must be reported ***within 24 hours*** of knowledge of the event by completing the AE/SAE eCRF. This will trigger an automatic notification of the SAE via an email communication to the sponsor and Fast-Track. Fast-Track will notify the Medical Monitor upon receipt of the notification and coordinate communications with the Medical Monitor.

11.1.9.2. 3-Day Supporting Documentation Requirements (Follow-up Report)

Written documentation for all SAEs must be received by the Medical Monitor within 3 days of reporting the event. Required eCRF that must be completed include the following:

- AE/SAE eCRF (revised if additional information is available)
- Concomitant Medication eCRF

In addition, paper copies of the following may be requested

- Copies of source documents pertinent to the event (laboratory reports, ECG tracings, medical chart notes, etc.). These should be identified only by subject number and not include any subject identification information prohibited by Health Insurance Portability Accountability Act (HIPAA).
- Any other relevant information necessary to support the investigator's judgment regarding the SAE's relatedness severity to the investigational product OR by request of the Medical Monitor/Alternate.

These paper documents may be submitted by facsimile, as email attachments, or by attaching them to the subject's eCRF casebook.

11.2. Collection and Processing of Blood for PK Determinations

Blood samples for determination of kindolor plasma concentrations will be collected by venipuncture within 15 minutes prior to dosing and at 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, 24, and 48 hours after dosing. Blood will be collected as close to nominal times as possible and the date and time that each blood sample is collected will be recorded to the minute.

[redacted]

All plasma samples for each cohort will be analyzed for AUC(Tlast) and Cmax before enrolling the next cohort. If $AUC_{(Tlast)}$ exceeds 87,550 ng.h/mL or C_{max} exceeds 13,490 ng/mL, then dose escalation will stop.

Further details on sample collection, processing, storage, and shipping are provided in the Manual of Procedures. Plasma concentrations will be determined using a validated liquid chromatography/mass spectrometry method.

11.3. Clinical Laboratory Tests

Clinical laboratory tests (Table 8) will be performed at the UCSD Medical Center clinical laboratory. The laboratory should be directly regulated by the College of American Pathologists (CAP) or Clinical Laboratory Improvement Act (CLIA) guidelines. The laboratory will need to provide a copy of current certification. Additional laboratory samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate additional testing to ensure safety.

Table 7: Clinical Laboratory Tests

Hematology	Clinical Chemistry	Coagulation	Urinalysis	Other
Hematocrit Hemoglobin RBC count WBC count Absolute counts for: Neutrophils Lymphocytes Monocytes Basophils Eosinophils Platelets	Albumin ALT AST BUN Creatinine Direct Bilirubin Total Bilirubin Alkaline phosphatase CPK LDH Sodium Potassium Chloride Calcium Bicarbonate Inorganic Phosphorus Uric Acid Total Cholesterol Total Protein Glucose Triglycerides	PT aPTT Fibrinogen INR	Specific gravity pH Ketones Protein Blood Glucose Nitrites Leukocyte esterase A microscopic evaluation will be performed if blood or leukocyte esterase are detected.	Amylase Lipase

Serum creatinine levels will be used to calculate creatinine clearance (CrCl) according to the Cockroft-Gault (1976) formula as follows:

Males $\quad CrCl\ (mL/min) = \dfrac{(140 - \text{age in years}) \times \text{body weight in kg}}{72 \times \text{serum creatinine mg/dL}}$

Females $\quad CrCl\ (mL/min) = \dfrac{0.85 \times (140 - \text{age in years}) \times \text{body weight in kg}}{72 \times \text{serum creatinine mg/dL}}$

In circumstances where creatinine clearance is overestimated when using actual weight in overweight patients, use ideal weight as the adjustment per standard practice. If estimated creatinine clearance is not overestimated using actual weight, use actual weight in the Cockcroft formula instead of the ideal body weight. This will avoid underestimations that may occur when using ideal body weight in the normal weight population while also reducing overestimations that may result when using actual weight in overweight individuals.

Ideal body weight may be used to adjust for subjects with a BMI of over 25 kg/m2 as needed:

Estimate Ideal body weight in (kg)
Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet.
Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.

For any laboratory test value outside the reference range that the investigator considers clinically significant:

- The investigator will repeat the test to verify the out-of-range value
- The investigator will follow the out-of-range value to a satisfactory clinical resolution
- A laboratory test value will be reported as an AE with the severity score assigned in accordance with the FDA Guidance for “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials”

11.4. Demographics

Demographics data include the subject’s age, gender, and race/ethnicity. These data will be collected by site staff on a source document and entered into an eCRF.

11.5. ECG

ECGs (12-lead resting) will be obtained in accordance with the schedule in Table 6. Any abnormalities will be noted and an assessment of clinical significance will be done by a study physician. The ECG obtained at Day 1 prior to dosing will serve as the baseline for subsequent comparisons. When an ECG is scheduled at the same time as a blood collection, the ECG will be obtained prior to the blood collection. An appropriately qualified physician (preferably a cardiologist) at the study site (local reader) will read all ECGs. The local reader will write on the ECG tracing his/her global interpretation as either "normal ECG," "abnormal ECG - not clinically significant" or "abnormal ECG – clinically significant," then sign and date the ECG. In addition, the reader will complete the ECG worksheet. Only the local reader's reading of the ECG will be collected. The automatic machine reading will not be collected. Heart rate, RR

interval, and QT intervals will be reported on an eCRF. QTcF will be calculated using the Fridericia correction factor [$QTcF = QT/RR^{(1/3)}$] (Fridericia-1920). The original ECG tracing will be retained in the subject's records at the study site.

11.6. Genetic Analysis

[redacted]

11.7. Fecal Occult Blood Tests

A FOBT will be performed to determine if any bleeding develops in the upper or lower GI tract. At the first screening visit, subjects will be provided with supplies and instructions on how to collect a stool sample and prepare a smear on a slide. The slide will be sent back to the clinical site laboratory for microscopic examination. A stamped and self-addressed mailer will be provided to the subject to return the specimen. If an FOBT is unable to be collected at intake day -1, the sample result from the closest bowel movement prior to subject dosing may be used.

11.8. Hepatitis and HIV Screen

Hepatitis A virus immunoglobulin M (HAV-IgM), hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab), and HIV antibodies (HIV Ab) tests will be performed at Screening. The laboratories performing these assessments should be directly regulated by the College of American Pathologists (CAP) or Clinical Laboratory Improvement Act (CLIA) guidelines.

11.9. Locator Form

After signing informed consent, subjects will be asked to provide names, addresses, and phone numbers of several friends and/or family members who can be contacted if the subject cannot be located (Locator Form). This locator form will be used to assist in contacting subjects between visits and at follow-up. This form asks subjects his/her name, address, and phone number and to provide names, addresses, and phone numbers of several friends and family members who can be contacted if the subject cannot be located. This information is essential and will be collected during screening and will be updated throughout the study as necessary. This information will remain exclusively at the site.

11.10. Medical/Surgical History

A complete medical history, including alcohol, tobacco and nicotine-containing and cannabis-containing product use histories will be taken at Screening for all potential study subjects to assure medical fitness. The medical history obtained at Screening will serve as the baseline for clinical assessment. Dates of prior surgeries will be recorded. The medical/surgical history will

be updated on Day -1 by asking the subject if anything has changed since the initial screening interview.

11.11. Pregnancy Test and Birth Control Record

An FDA-approved rapid result urine pregnancy test will be used (i.e., dipstick test). If applicable, subjects will be asked to sign a release of information form for study personnel to access medical records to obtain information regarding the outcome of a pregnancy that occurred during the study. The pregnancy test must be negative within the 72-hour period before clinic intake for the subject to be eligible for the study.

The Birth Control Assessment is designed to determine a female and male subject's compliance with the birth control specifications detailed in the inclusion criteria. Breast feeding status and sperm or ova donation status will be checked at screening, clinic intake, outpatient visits and final telephone contact.

11.12. Prior and Concomitant Medications

All medications taken by the subject 2 months prior to the start of screening, during the screening period, and through the final follow-up contact will be recorded on a source document and eCRF.

11.13. Physical Examination, Height, and Weight

A physical examination will be performed at Screening, and updated prior to dosing on Study Day 1, and prior to discharge from the site on Study Day 3 or upon premature termination. A symptom-directed physical examination will be performed, when necessary, at other times. Any significant physical examination findings after dosing will be recorded as an AE, if appropriate. Height will be measured only at Screening; the subject will not wear shoes. Body weight will be measured at Screening (for eligibility), prior to dosing on Study Day 1 (considered baseline weight for clinical assessment), at Day 7 or upon premature termination. The subject will wear lightweight clothing and no shoes during weighing. Height and weight will be recorded in cm and kg, respectively. BMI will be calculated as weight in kg divided by the square of height measured in meters.

11.14. SARS-CoV-2 Test

An FDA authorized SARS-CoV-2 antigen test will be performed within 72-hours before clinic intake and must be negative for the subject to be eligible for the study.

11.15. Screen Failures Documentation

To document the reason that a subject who consented to the study was not randomized, the Reasons the Subject Was Not Eligible eCRF will be completed for these subjects.

11.16. Subject Disposition

A subject disposition eCRF will be completed for all subjects who are randomized to the study and who are dispensed investigational product. This eCRF will be used to record the following

data as applicable: 1) completion status of the subject at the end of their participation and if they were discontinued early, and reason for early discontinuation.

11.17. Urine Drug Screen

An FDA cleared, CLIA waived 14-panel urine drug test card will be used to assess candidates for recent use of amphetamines, barbiturates, benzodiazepines, buprenorphine, cocaine, fentanyl, MDMA, methadone, methamphetamine, morphine, opioids, oxycodone, phencyclidine, and THC. Recent alcohol use will be assessed using an FDA cleared, CLIA waived ethyl glucuronide urine test strip.

11.18. Vital Signs

Vital signs to be assessed include sitting blood pressure, heart rate (after sitting for at least 3 minutes), oral temperature, respiration rate, and pulse oximetry in accordance with the schedule in Table 6. Blood pressure, heart rate, respiration rate, and pulse oximetry will be measured prior to any blood draws.

11.19. Urine Output

Urine output will be monitored over two 24-hour periods starting with the morning void on Day 1 and finishing through Day 3 prior to the morning void. The start time and end time of these two collection periods will be recorded and the amount collected during these 24-hour periods will also be recorded. As urine will also undergo other tests and some samples will be removed, the total volume during the collection period will be adjusted to account for any volumes removed for other tests. The timing of urine voids will also be recorded. Normal urine output is in the range of 800 – 2000 mL per 24-hour period. Urine output < 400 mL per 24 hours will be reported as an AE of oliguria. Urine output > 2500 mL per 24 hours will be reported as an AE of polyuria.

12. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

12.1. Statistical and Analytical Plans

Complete details of the statistical analyses to be performed will be documented in a statistical analysis plan (SAP), which will be completed prior to locking and unblinding the study data. This document will include more detail of planned statistical analyses as well as table, listing, and figure shells. Any changes to the final SAP will be outlined in the final study report.

12.2. Analysis Populations

The study analysis populations will consist of the following:

Safety: The safety population will include all subjects who received a dose of investigational product.

PK: The PK population will include subjects who received kindolor tosylate and had sufficient plasma concentrations to reliably calculate PK parameters.

12.3. Description of Statistical Methods

12.3.1. General Approach

For descriptive purposes, dichotomous and categorical variables will be presented as number of observations and percentages; continuous variables will be given as means, standard deviations (SD), median, minimum (min), and maximum (max). All data will be presented in listings.

12.3.2. Safety Analyses

AEs will be coded using the most recent version of the MedDRA and will be grouped by system organ class (SOC) and preferred term (PT) designation. The severity, frequency, and relationship of AEs to investigational product will be presented by SOC and PT groupings by Cohort and Treatment. Placebo subjects from all cohorts will be considered the placebo group. Listings of each individual AE including start date, stop date, severity, relationship, outcome, and duration will be provided. Each AE (based on PT) will be counted once only for a given study subject. If the same AE occurred on multiple occasions, the highest severity will be assumed. Thus, study subjects are not counted multiple times in a given numerator in the calculation of frequencies for a specific AE.

GI AEs will also be summarized separately including stool consistency scores and presence/absence and severity of other symptoms according to the GI Signs and Symptoms checklist or endoscopy results if applicable. The GI AE scale scoring will be presented as summary statistics by categorical response. The presence, absence, and severity of other signs and symptoms of GI AEs indicative of possible gastric inflammation or erosion including endoscopy results will be presented as numbers and percentages, including if the GI AE triggered a study stopping criteria.

Clinical laboratory test results, urine drug screen results, and pregnancy test results will be reported as summary statistics for each assessment time point. Clinical chemistry, amylase,

lipase, hematology, coagulation, urinalysis, FOBT, urine drug screen results, and pregnancy test results will be presented as summary statistics and change from baseline. In addition, change from baseline (shift tables) will also be presented for clinical chemistry, amylase, lipase, hematology, and coagulation data. Vital signs and ECG parameters will be presented as summary statistics and change from baseline. The proportions of ECG results considered clinically significant will also be provided. Urine output in mL/hour will be calculated over the two 24-hour period of collection and presented as summary statistics for both periods. All data will be presented by treatment group.

12.3.3. PK Analysis

The concentration-time profiles for kindolor will be evaluated by non-compartmental analysis. Actual sample times will be utilized for calculations. Calculations of parameters and comparisons will be performed with Phoenix WinNonLin 8.2 or higher (Pharsight Corporation, St. Louis, MO). The elimination rate constants (λ_z) will be estimated from the terminal log-linear decline in plasma concentrations and $t_{½}$ calculated as $\ln(2)/\lambda_z$. Area under the plasma concentration curves will be determined until the last time of a quantifiable plasma concentration (AUC_t) by the log/linear trapezoidal rule and to infinity (AUC_∞) based on the last plasma concentration (C_t) and λ_z. The value of T_{max} will be the observed time of the highest plasma concentration, and C_{max} would be the plasma concentration at that time. Mean, SD, geometric mean, median, minimum, and maximum plasma concentrations will be presented for each PK parameter. Concentration time curves by individual subject and by group geometric means ± SD will be presented.

12.3.4. Baseline Descriptive Statistics

Summaries of the characteristics of the subjects in each of the study groups at baseline will be prepared. A summary will be prepared to show dropouts/retention over time in each group, along with the reason for early termination.

12.3.5. *Ad Hoc* Analyses

Ad hoc analyses may also be performed.

12.3.6. Interim Analyses and Data Monitoring

An interim analysis of the safety data will be prepared as each cohort completes the study. As 2 placebo subjects will be included in each cohort, the safety data from all placebo subjects will be combined for each interim analysis.

12.4. Determination of Sample Size

The cohort size of 6 subjects receiving the active drug is generally accepted for first-in-humans clinical trials that provides a reasonable sample size for PK parameter estimates (Shen-2019). Administration of kindolor tosylate to 6 subjects in each dose group provides a 47%, 62%, 74%, or 82% probability of observing at least 1 occurrence of any AE with a true incidence rate for a given dose group of 10%, 15%, 20%, or 25%, respectively. Furthermore, it will be assumed that pooling the data for the subjects who received placebo (2 from each cohort) provides an adequately sized control group.

13. QUALITY CONTROL AND QUALITY ASSURANCE

This study will be conducted under International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and all applicable regulatory requirements.

Actions to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers; the review of protocol procedures with the investigator and study personnel prior to study start; the design of suitable source documents with appropriate instructions for use; the internal audit of source data according to GCP and internal procedures to ensure their accuracy, completeness, and verifiability; as well as the periodic site monitoring by the Sponsor's representatives (clinical monitors of Fast-Track Drugs & Biologics, LLC). Written instructions will be provided for collection, preparation, and shipment of blood samples. Clinical monitors will review source documents and eCRFs for accuracy and completeness during on-site monitoring visits; any discrepancies will be resolved with the investigator, as appropriate.

Significant and/or repeated noncompliance will be investigated, and remedial action instituted when appropriate. Failure to comply with remedial actions may result in study site termination and regulatory authority notification.

13.1. Study Monitoring

Study monitoring will be the responsibility of designated clinical monitors of Fast-Track. Monitors will assure compliance with the clinical protocol and ICH GCPs, human subject's protection, drug accountability, maintenance of the site regulatory file, and conformance of eCRF data with source documents. Monitoring visits by clinical monitors will be scheduled to take place at the initiation of the study, during the study at appropriate intervals, and after the last subject has completed the study. A report of monitoring observations will be provided to the PI (for corrective actions) and the Sponsor.

13.2. Audits and Inspections

Authorized representatives of the Sponsor, the FDA, and the IRB may visit the site to perform audits or inspections, including source data verification. The purpose of the audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines, and any applicable regulatory requirements.

The PI will contact the Sponsor's representative and Fast-Track if contacted by a regulatory agency about an inspection.

14. ETHICS

14.1. Ethics Review

The study will be conducted under a protocol reviewed by the site's IRB; the study is to be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study will ensure that the hazards do not outweigh the potential benefits; the results to be reported will be accurate; subjects will give their informed consent and will be competent to do so and not under duress; and all study staff will comply with the ethical principles in 21 Code of Federal Regulations (CFR) Part 50 and the Belmont Principles.

14.1.1. Review/Approval of Study Protocol

The study may not begin until the IND has been submitted to the FDA and the 30-day waiting period has expired without notification by FDA to the sponsor of any clinical hold issues. Lohocla Research Corporation will be the study sponsor. The site must obtain written approval from the IRB to conduct the study before study initiation. Lohocla Research Corporation will issue a formal authorization letter for the study to be initiated at the site. Progress reports will be submitted to the IRB by the investigator at the frequency requested by the IRB.

14.1.2. Protocol Modifications

All necessary protocol changes will be submitted in writing as protocol amendments to the IRB for approval prior to implementation. The sponsor will submit all protocol amendments to the FDA.

14.1.3. Protocol Deviation Reporting Procedures

All subject-specific deviations from the protocol are to be documented. The PI or designee will be responsible for identifying and reporting all deviations, which are occurrences involving a procedure that did not follow the study protocol. Any protocol deviation that adversely affects the safety or rights of a subject or scientific integrity of the study is considered a major deviation and will be reported immediately to the sponsor and the IRB.

14.2. Ethical Conduct of the Study

This study will be conducted in accordance with all applicable Federal human research protections requirements and the Belmont Principles of respect for persons, beneficence, and justice.

The procedures set out in this study are designed to ensure that the sponsor's representative and all study personnel abide by the principles of the ICH GCP Guideline and the Code of Federal Regulations (CFR). The PI confirms this by signing this study protocol and Form FDA 1572.

14.2.1. Confidentiality

14.2.1.1. Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that proprietary information furnished to clinical investigators and IRB will be kept confidential by the FDA only if maintained in confidence by the clinical investigator and IRB.

By signing this protocol, the investigator affirms to the sponsor that information furnished to the investigator by the sponsor will be maintained in confidence and such information will be divulged to the IRB or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees.

14.2.1.2. Confidentiality of Subject Records

To maintain subject confidentiality, all laboratory specimens, eCRFs, reports, and other records will be identified by a subject number only. Research and clinical records will be stored in a locked cabinet. Only research staff, the sponsor, and Fast-Track Drugs & Biologics clinical monitors will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by representatives of the sponsor. By signing the protocol, the investigator agrees that within local regulatory restrictions and ethical considerations, the sponsor or any regulatory agency may consult and/or copy study documents in order to verify eCRF data.

14.2.2. Compensation for Participation

Subjects will be compensated for travel expenses and for time contributed to this research study in the form of cash or vouchers. Compensation is detailed in the informed consent form.

14.2.3. Written Informed Consent

The informed consent process and document will be reviewed and approved by the IRB and sponsor's representative prior to initiation of the study. The consent document contains a full explanation of the possible risks, advantages, and alternate treatment options, and availability of treatment in the case of injury, in accordance with 21 CFR Part 50. The consent document indicates that, by signature, the subject permits access to relevant medical records by the sponsor's representative and by representatives of the FDA. The sponsor's representative will submit a copy of the initial IRB- and sponsor's representative-approved consent form to the FDA and will maintain copies of revised consent documents that have been reviewed and approved by the IRB.

A written informed consent document, in compliance with 21 CFR Part 50, 32 CFR Part 219, and the Belmont Principles, and HIPAA Authorization will be signed by the subject before any study-related procedures are initiated for each subject.

All potential subjects for the study will be given a current copy of the informed consent form to read. All aspects of the study and informed consent will be explained in lay language to the subject by either the investigator, or a medically trained designee. Any subject who is unable to

demonstrate understanding of the information contained in the informed consent form will be excluded from study participation.

All study subjects will be given a copy of the signed informed consent form.

14.2.4. Delegation of Responsibilities and Adequate Resources

The PI should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study.

The term "investigator" used throughout this protocol refers to the PI and/or qualified subinvestigators. The PI may delegate responsibilities to other study site personnel. The PI shall delegate tasks only to individuals qualified by education, training, and experience to perform the delegated tasks. The PI shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The PI is responsible for ensuring all delegated staff has been properly trained on the protocol and their assigned study responsibilities. A delegation log identifying all delegated duties and the individual to whom they have been delegated will be maintained at the study site.

14.2.5. Financial Disclosure

Clinical investigators are required to provide financial disclosure information for the submission of certification or disclosure statements required under 21 CFR § 54. As defined in 21 CFR § 54.2, a clinical investigator is a listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator. In addition, investigators must promptly update financial disclosure information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

15. DATA HANDLING AND RECORD KEEPING

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, laboratory results, data recorded in automated instruments, and pharmacy records, etc. This study will use an electronic data management system (EDMS) (IBM Clinical Development) and eCRFs. Data will be transcribed from source documentation into web-based eCRFs. The transcribed data will be consistent with the source document, or the discrepancies will be explained.

Clinical monitors will review all source records and compare them to the data entered into the eCRF. All entries, corrections, and alterations will be made by the investigator or other authorized study personnel. Any errors identified during monitoring will have a query posted by monitor for site staff to address. The EDMS system maintains a full audit trail of data entry, data corrections, and data queries.

15.1. Subject Identification and Confidentiality

Subjects will be identified on eCRFs by a unique subject number. No personal identifier will be used in any publication or communication used to support this research study. The subject number will be used if it becomes necessary to identify data specific to a single subject. The Sponsor's representative and designated clinical monitors of Fast-Track, the IRB, and the FDA are eligible to review medical and research records related to this study as a part of their responsibility to protect human subjects in clinical research. Personal identifiers will be removed from photocopied or electronic medical and research records.

15.2. Inspection of Records

The sponsor's representative or designee will be allowed to visit the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, investigational product stocks, drug accountability records, subject charts, study source documents, and other records relative to study conduct.

Subjects' health information is used to report results of research to the sponsor's representative and Federal regulators and may be reviewed during study audits for compliance with study plans, regulations, and research policies. The consent document indicates that by signature, the subject permits access to relevant medical records by the sponsor's representative and by representatives of the FDA.

Upon a subject's termination from the trial, completed eCRFs will be ready and available for on-site review by the sponsor's representative at scheduled monitoring visits.

15.3. Retention of Records

The investigator is responsible for creating and/or maintaining all study documentation required by Title 21 Code of Federal Regulations (21CFR) Parts 50, 54, 56, and 312, ICH E6 section 8, as well as any other documentation defined in the protocol. The investigator must provide key documents to the Sponsor prior to start of the study. A complete list of required regulatory documents will be provided in the study Manual of Procedures.

Federal and local regulations require that the investigator retain a copy of all regulatory documents and records that support the data for this study for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation.

The Sponsor will notify investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by the Sponsor that the entire clinical investigation (not merely the investigator's portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application/Clinical Trial Authorization or request for marketing approval (New Drug Application/Marketing Authorization Application).

If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with the Sponsor.

16. PUBLICATION POLICY

Review of manuscripts resulting from this study or from data generated during this study must occur according to the Publications Policy in the clinical trial agreement between the PI and Lohocla Research Corporation prior to submission for publication.

17. PROTOCOL SIGNATURE PAGE

SPONSOR REPRESENTATIVES

Typed Name	**Signature**	**Date**
[redacted]	_____	_____
Sponsor's Representative		

INVESTIGATORS

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse experiences as defined in section 11.1.9 of this protocol.

Typed Name	**Signature**	**Date**
Mark Wallace, MD	_____	_____
Principal Investigator		

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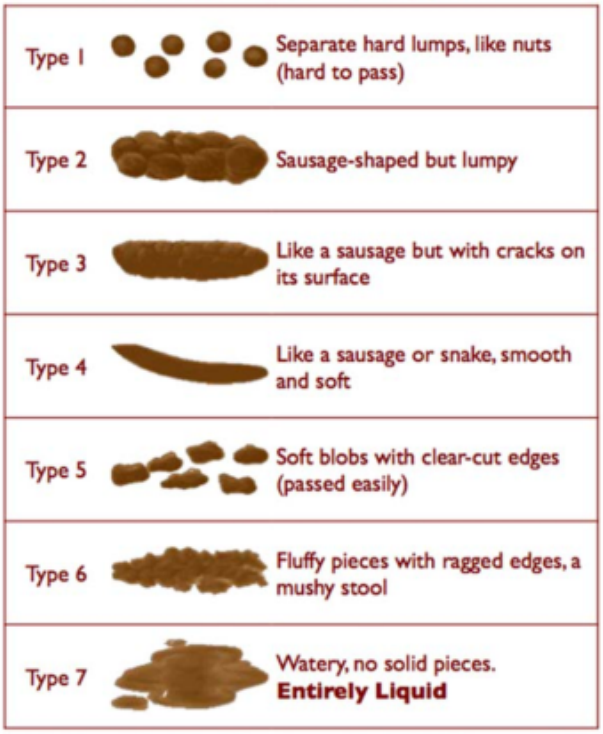
APPENDIX A. STOOL CONSISTENCY QUESTIONNAIRE

1. Frequency of stools per day:	☐☐			
2. Consistency of stools per day:	Using the Bristol Stool Chart - fill in the oval next to the consistency type that best matches your least firm ordinary BM prior to entering the study. ◯Type 1 ◯Type 2 ◯Type 3 ◯Type 4 ◯Type 5 ◯Type 6 ◯Type 7			
3. Category/ Symptom:	**0**	**1**	**2**	**3**
a. Urgency of stools	◯ No urgency	◯ Somewhat urgent	◯ Urgent	◯ Very urgent
b. Abdominal pain or discomfort	◯ No discomfort	◯ Mild - moderate discomfort	◯ Somewhat severe discomfort	◯ Very severe discomfort
c. Bloating	◯ No discomfort	◯ Mild - moderate discomfort	◯ Somewhat severe discomfort	◯ Very severe discomfort
d. Interference with performing normal; daily activities	◯ Not at all	◯ Some interference	◯ Much interference	◯ Incapacitating

BM= bowel movement

Bristol Stool Chart



APPENDIX B. GASTROINTESTINAL SIGNS AND SYMPTOMS CHECKLIST

The following signs and symptoms checklist will be reviewed each day starting with Day 1 after dosing, and then on Days 2, 3, and 7. Presence or absence of each sign or symptom will be recorded and if appropriate, an AE will be reported. With respect to laboratory tests and FOBT, criteria for clinical significance are provided and a yes/no response is required. If any of these are present prior to study drug administration, they will be reported with other medical history. The severity of the AEs will be in accordance with the FDA's Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

Signs/Symptom	**Present? (circle yes or no)**
Epigastric pain/discomfort (dyspepsia)	Yes / No
Fatigue	Yes / No
Light headedness	Yes / No
Postural dizziness	Yes / No
Syncope	Yes / No
Nausea	Yes / No
Vomiting	Yes / No
Hematemesis (vomiting blood)	Yes / No
Change in color of stool (melena)	Yes / No
Hematochezia (anal or rectal bleeding)	Yes / No
Clinically Significant Changes in Laboratory Tests	Yes / No
Positive FOBT	Yes / No
Decrease in hematocrit of at least 10 percentage points	Yes / No
Decrease in hemoglobin by at least 2 g/dL	Yes / No
Increase in BUN $\geq$ 40 mg/dL	Yes / No
Increase in creatinine $\geq$ 1.8 mg/dL	Yes / No
Increase in ALT $\geq$ 3 ULN	Yes / No
Increase in AST $\geq$ 3 ULN	Yes / No