Clinical Study Protocol

A Phase I, Double-Blind, Pharmacokinetic, Safety and Tolerability Study of Ketoprofen Lysine Salt Combined with Gabapentin (KLS-GABA) Compared to Ketoprofen Lysine Salt (KLS) Alone in Healthy Male Subjects (Part A) Followed by a Randomised, Double-Blind, Placebo-Controlled Study to Investigate the Pharmacodynamic Effects of KLS, and KLS in Combination with Gabapentin (GABA), in Healthy Male Subjects Using the Intradermal (ID) Capsaicin Model (Part B)

Investigational Medicinal Product: KLS-GABA

Sponsor Reference: KLG0120
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Sponsor: Dompé farmaceutici s.p.a.
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SPONSOR SIGNATURE PAGE

For and on behalf of the Study Sponsor:

PPD

Date: PPD

PPD

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Date PPD

INVESTIGATOR SIGNATURE PAGE

The undersigned confirm that the following Protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the study in compliance with the approved Protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, MAC and the Sponsor's (and any other relevant) Standard Operating Procedures (SOPs), and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical study without the prior written consent of the Sponsor.

I also confirm that I will, when required by the Sponsor, make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be provided; and that any discrepancies and serious breaches of GCP from the study as planned in this Protocol will be explained.

Principal Investigator:

Signature: PPD

Date: PPD

Dr Pui Man Leung MBChB MRCP(UK) FFPM DPM

SUMMARY OF CHANGES: CLINICAL STUDY PROTOCOL AMENDMENT 4 (VERSION 5.0)

This version of the protocol will supersede the previous version (Version 4.0, dated 27 May 2021).

The rationale for this substantial amendment is to address the grounds for non-acceptance of Version 4.0 of the Protocol from the Medicines Healthcare products Regulatory Agency (MHRA). Minor changes for spelling, grammar and punctuation have also been carried out where required, although these have not been described in the table below.

The changes to the protocol are detailed below:

Section	Description of Change
Section 6.2 (Page 42) – Exclusion Criteria (Part A)	**Previous text:** 7. AST, ALT, gamma-glutamyl transferase (GGT) or total bilirubin levels ≥1.5 × the ULN at screening. These laboratory evaluations may be repeated once at the discretion of the Investigator. If the repeat test is within the reference range, the subject may be included only if the Investigator considers that the previous finding will not introduce additional risk factors and will not interfere with interpretation of safety data. **Amended text:** 7. AST, ALT, gamma-glutamyl transferase (GGT) or total bilirubin levels ~~≥1.5 ×~~ above the ULN at screening. These laboratory evaluations may be repeated once at the discretion of the Investigator. If the repeat test is within the reference range, the subject may be included only if the Investigator considers that the previous finding will not introduce additional risk factors and will not interfere with interpretation of safety data.
Section 6.3 (Page 43) – Exclusion Criteria (Part B)	**Previous text:** 9. AST, ALT, GGT or total bilirubin levels ≥1.5 × the ULN at screening. These laboratory evaluations may be repeated once at the discretion of the Investigator. If the repeat test is within the reference range, the subject may be included only if the Investigator considers that the previous finding will not introduce additional risk factors and will not interfere with interpretation of safety data. **Amended text:** 9. AST, ALT, GGT or total bilirubin levels ~~≥1.5 ×~~ above the ULN at screening. These laboratory evaluations may be repeated once at the discretion of the Investigator. If the repeat test is within the reference range, the subject may be included only if the Investigator considers that the previous finding will not introduce additional risk factors and will not interfere with interpretation of safety data.

Strikethrough text indicates deletions. Underlined text indicates additions.

KEY STUDY CONTACTS

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SYNOPSIS

Study Title: A Phase I, Double-Blind, Pharmacokinetic, Safety, and Tolerability Study of Ketoprofen Lysine Salt combined with Gabapentin (KLS-GABA) compared to Ketoprofen Lysine Salt (KLS) Alone in Healthy Male Subjects (Part A) Followed by A Randomised, Double-Blind, Placebo-Controlled Study to Investigate the Pharmacodynamic Effects of KLS, and KLS in Combination with Gabapentin (GABA), in Healthy Male Subjects using the Intradermal (ID) Capsaicin Model (Part B).

Investigational Medicinal Product: KLS-GABA

Clinical Phase: I

Objectives:

Part A

The primary objective of this study is to determine the single dose pharmacokinetics (PK) of ketoprofen lysine salt combined with gabapentin (KLS-GABA [80 mg-34 mg]) compared to KLS alone (80 mg) in healthy male subjects.

The secondary objective of this study is:

- To determine the safety and tolerability of a single oral dose of KLS-GABA (80 mg-34 mg) compared to KLS alone (80 mg) in healthy male subjects.

Part B

The primary objective of this study is to determine the pharmacodynamic (PD) effects of KLS-GABA in the Intradermal (ID) capsaicin model in healthy male subjects.

The secondary objectives of this study are:

- To further investigate the safety, tolerability, and PK of single oral doses of KLS-GABA and KLS alone.
- To investigate the possible relationship between plasma levels of drug and efficacy in pain reduction.

Endpoints:

Part A

The primary endpoints are plasma PK concentrations and parameters of ketoprofen alone when administered as KLS and ketoprofen and gabapentin when administered as KLS-GABA, including but not limited to: area under the concentration-time curve (AUC), from zero to the last quantifiable concentrations (AUC_{0-t}), AUC from zero to infinity ($AUC_{0-\infty}$), AUC from zero to 12 hours postdose (AUC_{0-12h}), AUC from zero to 24 hours postdose (AUC_{0-24h}), AUC from zero to 36 hours postdose (AUC_{0-36h}), AUC from zero to 48 hours postdose (AUC_{0-48h}), maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}) and half-life ($t_{1/2}$) in healthy male subjects.

The secondary endpoint of the study is the clinical safety data from adverse event (AE) reporting, 12-lead electrocardiogram (ECG), vital signs (supine blood pressure, heart rate, oral temperature), clinical laboratory evaluations (chemistry, haematology, urinalysis and coagulation) and physical examinations in healthy male subjects.

Part B

The primary endpoint is:

- Analgesia/reduction in pain post capsaicin injection from the ID capsaicin model.

The secondary endpoints are:

- Subjective rating of pain from the ID capsaicin model.
- Pain score of hyperalgesia from the ID capsaicin model.
- Area and pain score of brush-evoked allodynia from the ID capsaicin model.
- Area of flare (AF) from the ID capsaicin model.
- Plasma PK concentrations.

- Clinical safety data from AE reporting, 12-lead ECG, vital signs (supine blood pressure, heart rate, oral temperature), clinical laboratory evaluations (chemistry, haematology, urinalysis, and coagulation) and physical examinations in healthy male subjects.

Study Design:

This is a 2-part, randomised study.

Part A

Part A is a randomised, double-blind, crossover group study to investigate the safety, tolerability, and PK profile of a single oral dose of KLS-GABA compared to KLS alone in healthy male subjects. It is planned to enrol 12 subjects. All subjects will take part in 2 treatment periods, in which they will be randomised to receive either a single dose of KLS-GABA (80 mg-34 mg) or a single dose of KLS (80 mg) alone in each treatment period.

Subjects' participation in Part A will last approximately 7 weeks and will consist of the following:

- A screening visit (up to 28 days prior to Day 1 of Treatment Period 1),
- Admission to the clinical research unit (CRU) on Day -1 prior to Treatment Period 1,
- Treatment Period 1 (Day 1 to Day 3),
- A washout period of a minimum of 7 days,
- Admission to the CRU on Day -1 prior to Treatment Period 2,
- Treatment Period 2 (Day 1 to Day 3),
- A follow-up visit (5 to 7 days post-final dose following Treatment Period 2).

Safety will be assessed through AE reporting, 12-lead ECGs, vital signs, physical examinations, and clinical laboratory examinations. Pharmacokinetics will be assessed by blood sampling.

Part B

Part B is a randomised, double-blind, placebo-controlled parallel group study to investigate the PD effects, PK/PD correlation, safety, and tolerability of three single oral dose levels of KLS-GABA compared to KLS alone, 300 mg gabapentin and placebo in the ID capsaicin model in healthy male subjects.

It is planned to enrol 128 subjects, randomised evenly to 8 possible treatments; subjects will receive either KLS alone, KLS-GABA, 300 mg gabapentin or placebo. The planned treatments are:

- KLS alone (40 mg, 80 mg, or 160 mg)
- KLS-GABA (40 mg-17 mg, 80 mg-34 mg or 160 mg-68 mg)
- Gabapentin (300 mg)
- Placebo

Subjects' participation in Part B will last approximately 6 weeks and will consist of the following:

- A screening visit (up to 28 days prior to dosing),
- An additional screening visit (at least 7 days prior to dosing) to determine the subject's response to capsaicin and to familiarise them in the pain measurements,
- Admission to the CRU on Day -1, for collection of pain measurements and completion of the ID capsaicin model,
- A treatment period (morning of Day 1 until 12 hours postdose),
- Discharge from the CRU 12 hours postdose,
- A follow-up visit (5 to 7 days postdose).

Safety will be assessed through AE reporting, 12-lead ECGs, vital signs, physical examinations, and clinical laboratory examinations. Pharmacokinetics will be assessed by blood sampling. Pharmacodynamics will be assessed using the ID capsaicin model and pain measurements.

Treatment Duration:

Part A: 2 days (Day 1 in Treatment Period 1; Day 1 in Treatment Period 2)

Part B: 1 day (Day 1)

Study Participants:

Part A

Healthy male subjects, with a body mass index (BMI) of 18 to 32 kg/m^2 (inclusive), of any ethnic origin. Subjects in Part A should be aged between 18 to 55 years, inclusive. Subjects must have a negative test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at Screening and Day -1 of each treatment period.

Part B

Healthy male subjects, with a BMI of 18 to 32 kg/m^2 (inclusive), with a skin type compatible with capsaicin measurements without significant skin allergies, pigmentary disorders, or any active dermatological conditions that might interfere with the conduct of the study. Subjects must not have any skin trauma, any active skin disorder, significant scarring, skin disease or tattoos on either forearm, or a significant history of trauma or skin disease in either arm. Subjects in Part B should be aged between 18 to 55 years, inclusive. Subjects must be able to tolerate capsaicin injection at Screening, and must not have a known intolerance to capsaicin, hot peppers, or any excipient in the IMP. Subjects should not have a history of neurological disorders or chronic pain conditions which may impact the perception of pain or impairs the subject's ability to fully participate in the study. Subjects must have a negative test for SARS-CoV-2 at Screening and Day -1.

Dose and Route of Administration:

Subjects will be fasted overnight prior to dosing until 3 hours postdose. Water will be allowed ad libitum except for 1 hour before and 3 hours after dosing.

Part A

KLS 80 mg capsules or KLS-GABA 80 mg-34 mg capsules will be administered once in the morning of Day 1 in Part A in Treatment Periods 1 and 2 in the fasted state, according to the randomisation schedule. Capsules will be administered with 240 mL of water.

Part B

The planned treatments are:

- KLS alone (40 mg, 80 mg or 160 mg)
- KLS-GABA (40 mg-17mg, 80 mg-34 mg, or 160 mg-68 mg)
- Gabapentin (300 mg)
- Placebo

The active IMP (KLS, KLS-GABA, or gabapentin in Part B) or placebo will be administered as capsules once in the morning of Day 1 in the fasted state. Subjects assigned to receive 160 mg KLS alone will be administered two KLS 80 mg capsules, and subjects assigned to receive 160 mg-68 mg KLS-GABA will be administered two co-crystal KLS-GABA 114 mg (80 mg-34 mg) capsules. To maintain the blind, subjects assigned to receive either 40 mg KLS alone, 80 mg KLS alone, 40 mg-17 mg KLS-GABA, 80 mg-34 mg KLS-GABA or 300 mg gabapentin will also receive a placebo capsule (dummy placebo). Subjects assigned to receive placebo will receive 2 placebo capsules. Capsules will be administered with 240 mL of water.

Criteria for Evaluation:

Part A

Safety will be assessed through AE reporting, 12-lead ECGs, vital signs, physical examinations, and clinical laboratory evaluations. Pharmacokinetics will be assessed by blood sampling.

Part B

Pharmacodynamics will be assessed through pain measurements (response to ID injection of capsaicin, measurement of pain using a visual analogue scale, area and pain score of hyperalgesia, area and pain score of allodynia, and AF) and the ID capsaicin model. Safety will be assessed through AE reporting, 12-lead ECGs, vital signs, physical examinations, and clinical laboratory evaluations. Pharmacokinetics will be assessed by blood sampling.

Statistical Analysis:

The Study Statistical Analysis Plan with more technical and detailed elaboration of the principal features of statistical analyses will be finalised before database lock. Any deviation from the original statistical plan will be described in the Clinical Study Report.

No formal sample size calculation has been performed. A study of 12 subjects in Part A and 128 subjects in Part B is considered to be sufficient to meet the objectives of the study.

Summary statistics have been defined for quantitative variables (number of observations, mean, standard deviation, median, minimum and maximum) and qualitative variables (number and percentage per category).

Safety parameters and subjects' characteristics will be listed and summarised using descriptive statistics.

Subject disposition will include a summary of the number and percentage of patients entered, enrolled, and treated as well as number and percentage of patients completing the study, or discontinuing. A summary of all protocol deviations will be provided.

Demographic and baseline characteristics, medical history, concomitant medication and treatment compliance will be summarised for all subjects by treatment.

AEs will be presented in terms of the number of AEs and incidence. Standard laboratory evaluations, vital signs, physical examinations, and 12-lead ECG parameters will be summarised by treatment at each available time point.

For Part A, PK parameters estimates will be calculated by noncompartmental methods. Pharmacokinetic data will be listed for each subject, along with summary statistics. A comparison of the main PK parameters obtained (C_{max}, AUCs, t_{max} and $t_{1/2}$) after KLS-GABA and ketoprofen administration will be presented. For Part B a PK/PD correlation will be implemented for all administered doses.

In Part B, the response to ID injection of capsaicin will be assessed in 6 ways (subjective rating of pain, area and pain score of hyperalgesia, area and pain score of brush-evoked allodynia and area of flare) and summarised using descriptive statistics.

Mixed Model Repeated Measures (MMRM) will be fit to data for each PD parameter using two groups of models. Group 1 will assess longitudinal changes in Scores / Area against baseline. Group 2 will assess differences in Scores / Area between treatments for each timepoint.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADME	absorption, distribution, metabolism and excretion
AE	adverse event
AF	area of flare
ALP	alkaline phosphatase
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
$AUC_{0\text{-}12h}$	area under the plasma concentration-time curve from zero to 12 hours postdose
$AUC_{0\text{-}24h}$	area under the plasma concentration-time curve from zero to 24 hours postdose
$AUC_{0\text{-}36h}$	area under the plasma concentration-time curve from zero to 36 hours postdose
$AUC_{0\text{-}48h}$	area under the plasma concentration-time curve from zero to 48 hours postdose
$AUC_{0\text{-}t}$	area under the plasma concentration-time curve from zero to the last quantifiable concentration
$AUC_{0\text{-}\infty}$	area under the plasma concentration-time curve from zero to infinity
BMI	body mass index
BP	blood pressure
CI	confidence interval
C_{max}	maximum plasma concentration
CNS	central nervous system
COVID-19	Coronavirus disease 2019
COX	cyclo-oxygenases
CRO	Contract Research Organisation
CRU	clinical research unit
DRESS	drug rash with eosinophilia and systemic symptoms
ECG	electrocardiogram
eCRF	electronic case report form
EudraCT	European Union Drug Regulating Authorities Clinical Trials
λz	terminal rate constant
FDCs	fixed-dose combinations

GABA	Gabapentin
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HED	human equivalent dose
HIV	human immunodeficiency virus
HR	heart rate
IASP	International Association for the Study of Pain
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ICF	informed consent form
ID	intradermal
IMP	investigational medicinal product
KLS	Ketoprofen Lysine Salt
LLOQ	lower limit of quantification
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
NRS	numeric rating scale
NSAIDs	non-steroidal anti-inflammatory drugs
OTC	over-the-counter
PD	Pharmacodynamic
PK	pharmacokinetic
PT	preferred term
QTcF	QT interval corrected for heart rate using Fridericia's formula
REC	research ethics committee
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-Cov-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation

SJS	Steven-Johnson Syndrome
SmPC	Summary of Product Characteristics
SOC	system-organ class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
$t_{1/2}$	half-life
TEN	toxic epidermal necrolysis
t_{max}	time to maximum plasma concentration
ULN	upper limit of normal
VAS	visual analogue scale
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

Pain is a complex and multifactorial medical condition defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage".[1] It is the most common reason for physician consultation in most developed countries,[2] and can have a strong impact on patient's activities of daily living and quality of life.

Acute pain is a physiologic response to noxious stimuli that is usually transitory and time limited,[3] acute pain requires treatment for a few weeks but often the administration of a single drug is not sufficient to reach pain relief and many patients with acute pain will not obtain an acceptable analgesia.[4] Untreated or inadequately treated acute pain can determine patient frustration, improved cost of therapies, prolonged hospitalisation, and generally progression of acute pain to chronic pain.

Chronic pain is considered a distinct entity with its own medical characterisation and taxonomy and is generally a consequence of a disease or damage. Targeted prevention and management approaches of chronic pain should take into account a number of factors (such as the biological, psychological, socio-demographic, and lifestyle determinants and outcomes of pain) and provide comprehensive and multidisciplinary treatments, including pharmacotherapy.

Non-opioid medications are currently considered as the first line therapy for chronic pain; indeed, considering the recent epidemic of opioid use in the United States,[5] opioids or combination drugs containing opioids should be used for treatment of moderate to severe pain for which alternative therapies are unsatisfactory.

According to its pathophysiology, pain was described as either nociceptive or neuropathic; these differ in terms of onset and expression; in general, nociceptive pain is associated with acute pain, whereas neuropathic is more frequently chronic. However, this division excluded many patients. The term "mixed pain" has never been formally defined and does not appear in the IASP taxonomy even if it is increasingly recognised and accepted by clinicians and used in the scientific literature to describe a combination of nociceptive and neuropathic components.

An international group of specialists addressed this question, proposing the following definition "Mixed pain is a complex overlap of the different known pain types (nociceptive, neuropathic, and nociplastic) in any combination, acting simultaneously and/or concurrently to cause pain in the same body area. Either mechanism may be more clinically predominant at any point of time. Mixed pain can be acute or chronic".[6]

Patients experiencing mixed pain have more comorbidities such as depression, anxiety and sleep disorders, more adverse psycho-social factors, a lower health-related quality of life and shows a greater clinical complexity that negatively impact on response to the treatment.[7]

A number of common pain states are considered to be mixed pain conditions including the following: cancer pain, lower back pain, osteoarthritis pain, postsurgical pain, chronic joint pain and pain in primary care.[6] The phenotypical complexity of mixed pain makes its evaluation, diagnosis and above all treatment, significantly challenging; no clear guidelines specific to mixed pain are presently available and, thus, the best guidance on treatment decision-making derives only from treatment approvals for neuropathic pain.[8]

An individualised, multimodal therapy which target potentially both nociceptive and neuropathic pain components represents a rational approach to address this unmet medical need.[9]

Although drug combination is commonly empirically adopted in clinical practice, prospective studies regarding the relative efficacy and safety of therapeutic drug associations to treat various painful conditions are still few,[10] and more preclinical, clinical, and translational studies are needed to improve the efficacy of combination drug therapy.[11]

Multimodal engagement can be reached through different methods. To date, these have included treatments with open combinations of two or more concomitant drugs, fixed-dose combinations (FDCs), or multimodal agents. Each of these approaches present benefits and limitations: the use of open combinations allows personalised treatment but can also lead to decreased compliance. On the other hand, FDCs offer a more standardised approach, improve patient compliance and reduce costs but do not permit an individualised approach.

A new method to achieve multimodal pharmacotherapy comprises the development of an innovative type of pharmaceutical co-crystal. A co-crystal is formed by an active pharmaceutical ingredient (API) and a second component contained within a single, unique crystal structure. Currently available pharmaceutical co-crystals contain a single API and a nonactive co-crystal former (coformer) in the same crystal structure but could also contain more than one API ("API–API co-crystals").[12]

Co-crystals of ketoprofen, lysine and gabapentin are in development, have more than one API and might offer the potential to provide benefits beyond the simple combination of the constituent APIs therein, as well as a reduced pill burden and improved compliance. The salt of ketoprofen is a well-known and established non-steroidal anti-inflammatory drug (NSAID) and gabapentin is a gamma-butyric mimetic compound with an antiepileptic and peripheral neuropathic analgesic activity. Changes in physico-chemical characteristics of constituent APIs can lead to clinical benefits more efficiently than individual ketoprofen lysine salt (KLS) and gabapentin, with a better gastric tolerability profile, as already evidenced by preclinical models.

From the safety data available for the two products, the combination of ketoprofen, lysine and gabapentin (KLS-GABA) does not pose any safety concern. The dose of ketoprofen will not exceed the current prescribed doses as per the Summary of Product Characteristics (SmPC), and the gabapentin dose will be at least 10-15-fold lower than the dose prescribed for neuropathic pain or epilepsy (up to 1800 mg/day). Furthermore, gabapentin is not metabolised by hepatic enzymes and is almost completely excreted by the kidney as the parent drug; therefore, there is no drug-drug metabolic interaction foreseen. In summary, co-crystal of ketoprofen, lysine and gabapentin might become an advantageous addition to the current armamentarium against acute and chronic pain and could be particularly effective in mixed pain, matching two different mechanisms of action.

From a regulatory view, according to the International Conference on Harmonisation (ICH) guideline M3(R2) for combination drugs which are both late stage products, there are no causes for toxicological concern based on the available data, although there is no clinical experience with co-administration. Nonclinical combination studies generally are not recommended to support small-scale clinical Phase II studies up to a duration of 3 months. Combination toxicity studies will be necessary for clinical Phase III studies and for marketing.

The ICH guideline M3(R2) did not require toxicity studies to be performed before the administration of the drug combination to humans, however Dompé voluntarily carried out a pharmacokinetics (PK) and tolerability study in minipigs by oral administration.

1.2. Study Rationale

The co-crystal KLS-GABA showed its ability to reduce mechanical allodynia, thermal hyperalgesia and oedema formation very efficiently in several preclinical studies in inflammatory and chronic pain models.

Human experimental pain models are useful in understanding the mechanisms underlying clinical pain conditions and can be used to test the analgesic efficacy of drugs used in the management of pain. Furthermore, the use of pain models excludes confounding variables due to coexisting fever, general malaise, and psychological cognitive and social aspects of illness.[13]

The capsaicin model is the most widely used model to mimic the symptoms of neurogenic hyperalgesia as observed in neuropathic pain.[14]

Capsaicin, an active component of hot peppers, exerts its hyperalgesic effects via transient receptor potential cation channel subfamily V member 1 receptor activation. The intradermal (ID) injection of capsaicin induces a localised release of substance P (neurokinin 1), calcitonin gene related peptide and other neuropeptides resulting in localised hyperaemia (flare), hyperalgesia, and allodynia. These effects are similar to those seen in neuropathic pain. Furthermore, ID capsaicin has been found to have a dose-dependent relationship with flare, allodynia and hyperalgesia responses in pain-free volunteers,[15] and has been shown to detect the effects of a single dose of pregabalin in healthy volunteers.[16] Therefore, the ID capsaicin model is a potentially useful tool to study the mechanisms of neuropathic-type symptoms and the efficacy of analgesic drugs in relieving these symptoms, such as ketamine, magnesium, lidocaine, alfentanil, diclofenac, orphenadrine, gabapentin, cannabis, lamotrigine, H1 antagonists, hydromorphone, and the lidocaine.[17]

According to the current literature, calcium channel α2-δ ligands and opioids, anaesthetics, and N-methyl D-aspartate receptor antagonists seem to have an attenuating effect on capsaicin-induced hyperalgesia to mechanical stimuli. Non-steroidal anti-inflammatory drugs and other compounds showed no, or very limited, efficacy in attenuating capsaicin-induced hyperalgesia.[18-22]

As proof of concept, the co-crystal of KLS and gabapentin could demonstrate an attenuation of secondary effects induced by a model commonly used and accepted as a paradigm of clinical neuropathic pain.

1.3. Non-Clinical Experience

1.3.1. Pharmacodynamics

Peripheral inflammatory pain was studied in the rat. Peripheral inflammatory pain was induced in the left hind paw of each animal by a single intra-plantar injection of 1% λ-carrageenan vehicle, and drugs were orally administered 1 hour before the carrageenan injection. The animal's paw volume, mechanical allodynia and thermal hyperalgesia were measured respectively by plethysmometer, von Frey filaments (mechanical allodynia) and a hot plate test (thermal hyperalgesia), and were performed before (0 hour) and post injection of carrageenan at multiple time points (1, 2, 3, 4, 5 and 6 hour post-carrageenan).

The activity of co-crystal of ketoprofen, lysine and gabapentin (67.5 mg/kg) was compared to the activity of KLS (47.1 mg/kg), gabapentin (20.4 mg/kg), KLS with gabapentin (47.1 and 20.4 mg/kg); all the compounds were orally administered 1 hour prior to carrageenan injection in gelatine capsules while indomethacin (10 mg/kg), used as a reference standard, was orally administered as solution.

A time-dependent paw swelling was observed starting from 1 hour, with a peak of oedema formation at 6 hours post-carrageenan injection. The co-crystal significantly inhibited oedema formation from 3 hours to 6 hours post carrageenan, with a more pronounced effect as compared to all the other tested compounds, as shown in Figure 1.

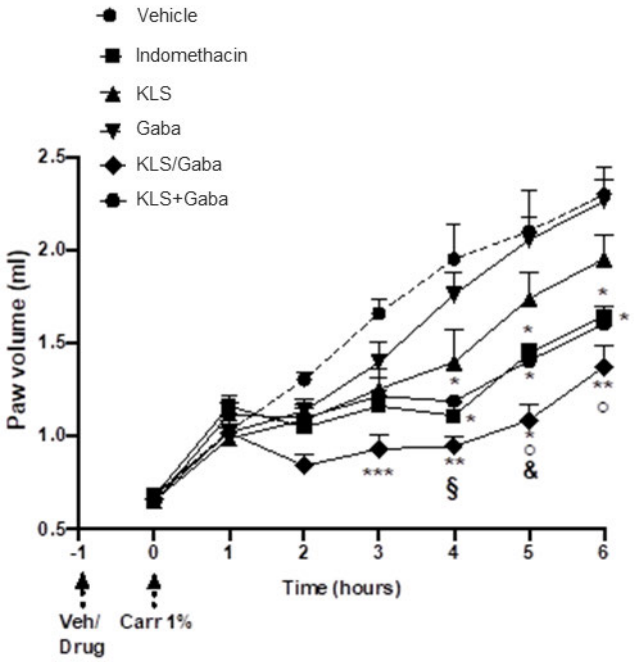

Figure 1: Effect of oral administration of KLS/Gabapentin co-crystal, KLS, Gabapentin and KLS with Gabapentin on carrageenan-induced paw oedema.

Time-course of anti-inflammatory effect of KLS/Gaba co-crystal or KLS with Gaba combinations compared with KLS, Gaba, Indomethacin or Vehicle on rat paw swelling (ml) after intra-plantar injection of 1% carrageenan Each time point represents the mean ± SEM of four-six (vehicle)/eight (drugs) rats. Black arrows indicate vehicle/drugs or carrageenan injection. P<0.05 was considered as statistically significant and calculated by using two-way ANOVA followed by Tukey's post-hoc test. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 vs Vehicle, p<0.05 vs Indomethacin, &p<0.05 vs KLS, §p<0.05 vs KLS with Gaba.

Under the same experimental conditions, mechanical allodynia was evaluated by von Frey filament. Mechanical withdrawal threshold significantly decreased in the ipsilateral paw starting from 1 hour after carrageenan and the decrease was maintained until the end of the observation period (6 hours). Also in this case, the co-crystal induced a stronger antiallodynic activity from 1 to 5 hours as compared to the other drugs (Figure 2).

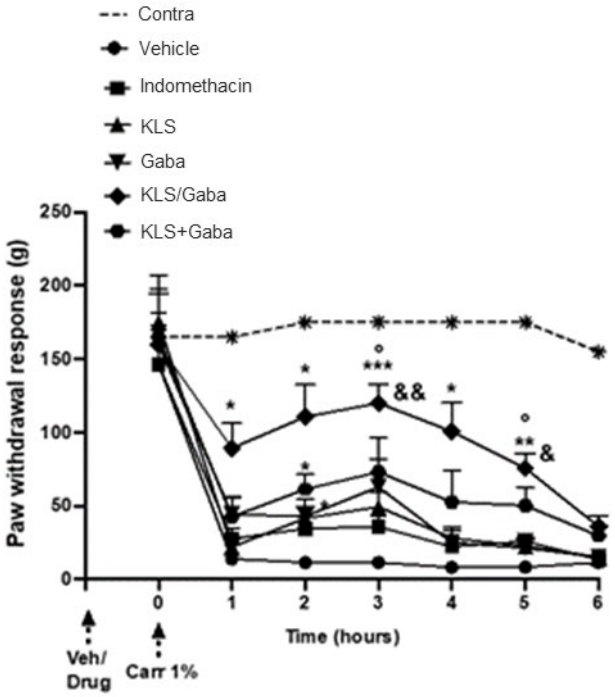

Figure 2: Effect of oral administration of KLS/Gabapentin co-crystal, KLS, Gabapentin and KLS with Gabapentin on carrageenan-induced mechanical allodynia.

Time-course of the analgesic effect of KLS/Gabapentin co-crystal or KLS with Gabapentin combinations compared with KLS, Gabapentin, Indomethacin or Vehicle on rat paw swelling (mL) after intra-plantar injection of 1% carrageenan. Each time point represents the mean ± SEM of four-six (vehicle)/eight (drugs) rats. Black arrows indicate vehicle/drugs or carrageenan injection. P<0.05 was considered as statistically significant and calculated by using two-way ANOVA followed by Tukey's post-hoc test. *p<0.05, **p<0.01, ***p<0.001 vs Vehicle, p<0.05 vs Indomethacin, $^{\&}$p<0.05, $^{\&\&}$p<0.01 vs KLS with Gabapentin.

Furthermore, a tendency to reduce thermal hyperalgesia was measurable in the co-crystal group compared to the other treatment groups.

In conclusion, the co-crystals anti-inflammatory activity was proven to be more effective as compared with the other tested compounds, both when they were given alone as single compound (KLS- and gabapentin-treatment group) or administered together (KLS with gabapentin-treatment group). These results show that the co-crystal yields an antinociceptive synergistic activity that might be useful in the treatment of inflammatory pain.

A study was undertaken to comparatively evaluate the effects of the co-crystal of ketoprofen, lysine and gabapentin (67.5 mg/kg), KLS (47.1mg/kg), gabapentin (20.4 mg/kg), KLS with gabapentin (47.1 and 20.4 mg/kg) in a model of post-incisional pain in rats.

Gabapentin was also used as reference standard; in this case, it was orally administered as a solution at a dose of 100 mg/kg.

Briefly, after anaesthesia, an incision with a length of 1 cm was made through skin and fascia of the plantar aspect of the paw, starting 0.5 cm from the proximal edge of the heel and extending toward the toes. The skin and fascia were elevated and incised longitudinally. Following haemostasis with gentle pressure, the skin was sutured by using 5–0 nylon. The control rats received a sham procedure, which consisted of anaesthesia administration but without incision (n=4).

Mechanical allodynia (von Frey filaments), mechanical hyperalgesia (Randal-Selitto paw pressure technique) and thermal hyperalgesia (hot plate test) were evaluated.

At the end of behavioural experiments, all animals were sacrificed with a lethal dose of urethane, and ulcerogenic activity in the stomach was evaluated. The stomachs were removed and opened by cutting along the greater curvature. Gastric lesions in each rat were evaluated by an arbitrary scale as follows: 0: no lesion, 1: haemorrhage erosion and damaged mucous, 2: from 1 to 4 lesions under 3 mm, 3: over 5 lesions under 3 mm or a single lesion above 3 mm, 4: over 2 lesions above 3 mm, 5: lesions with pore. The ulcerogenic activity was calculated by comparing the ulcerogenicity scores in the drug-treated groups with those in the vehicle-treated animals.

An incision of the plantar surface of the hind paw led to an induction of thermal and mechanical hyperalgesia measured by the hot plate and Randal-Selitto test. Paw withdrawal latency(s) and threshold (g) significantly decreased starting from 3 hours up to 24 hours post-injury (the latest time point monitored in this study) as shown in Figure 3.

The single dose administration of co-crystal completely blocked the development of thermal hyperalgesia throughout the observation period; similarly, co-crystal completely abolished mechanical hyperalgesia up to 5 hours after surgery, maintaining a very pronounced effect up to 24 hours. On mechanical hyperalgesia, the effects of co-crystal observed at 3 and 5 hours (100% of inhibition) significantly differed from those produced by all the other compounds (40% and 51,3% for KLS with GABA; 58.5 and 42.2% for GABA; 42.5 and 44,2% for KLS; 81.8% and 75.4% for Gabapentin, respectively at 3 and 5 hours).

Observations of the surface of the stomach under a dissecting microscope (1.8x) with square–grid eye revealed that the only group showing gastrointestinal damage was KLS-treated animals. Indeed, this group showed haemorrhagic red spots on gastric mucosa, but no congestion, erosion or ulceration were observed (Figure 3). Thus, value for the ulcer index was 1 for KLS animals. On the contrary, injured rats treated with Gabapentin (orally administered as solution at a dose of 100 mg/kg), Gaba, KLS with Gabapentin or KLS/Gabapentin co-crystal did not display gastric ulcerogenic signs, similarly to the control group; the ulcer index for these groups was 0 (Figure 3).

In conclusion, the co-crystal produced better pain relief and showed a better gastric tolerability profile than KLS and Gabapentin in this model of postsurgical pain.

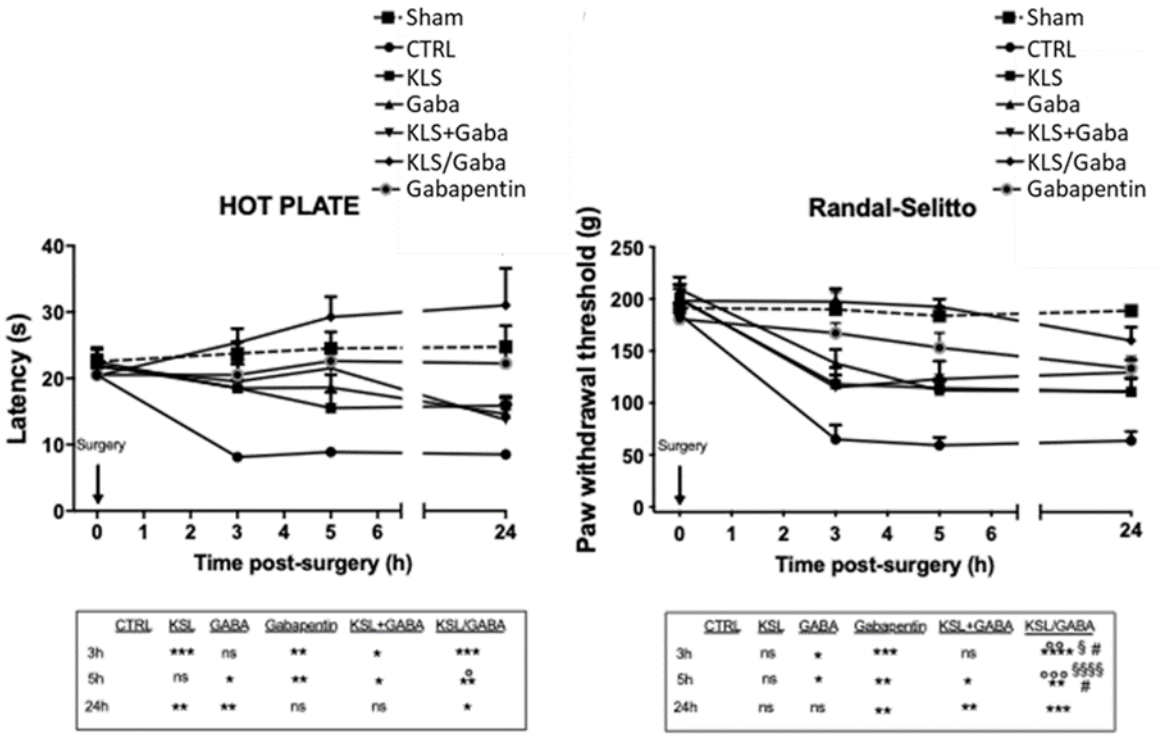

Figure 3: Time-course of analgesic activity of KLS, gabapentin, KLS with Gabapentin (KLS + Gaba) and co-crystal of Ketoprofen, Lysine and Gabapentin (KLS/Gaba) administered in capsules compared to Gabapentin (100 mg/kg, oral solution) or vehicle on thermal hyperalgesia (A) and mechanical hyperalgesia (B) in a rat model of post-incisional pain.

Each time point represents the mean ± SEM of four (vehicle)/eight (drugs) rats. Black arrow indicates surgery induction. P<0.05 was considered as statistical significance and calculated by using two-way ANOVA followed by Tukey's post-hoc test for comparisons between groups, or one-way ANOVA followed by Tukey's post-hoc test for comparisons within groups. *p<0.05, **p<0.01, ***p<0.001 ****p<0.0001 vs CTRL; p<0.05, p<0.01, p<0.001 vs KLS; §p<0.05, §§§§p<0.0001 vs Gaba, #p<0.05 vs KLS and Gabapentin.

1.3.2. Pharmacokinetics

Preliminary PK of the KLS-GABA co-crystal (DFL24412) has been studied in rats after administration of gelatine capsules (size 9, Torpac®: 2 capsules for each animal corresponding to 56.9 mg/kg of KLS-GABA co-crystal).

Table 1: Main Pharmacokinetic Parameters of KLS/Gabapentin Co-crystal (DFL24412) Obtained After Single Capsule Administration in Sprague-Dawley Rats (Mean ± SD).

Test Item	C_{max} µg/mL	AUC_{tot} h·µg/mL	AUC_{0-24h} h·µg/mL	MRT h	$t_{1/2}$ h	t_{max} h
Ketoprofen	32.6 ± 18.8	460.3[a] ± 109	368.6 ± 102.0	11.7 ± 2.9	17.0 ± 5.5	11.1 ± 12
Gabapentin	6.7 ± 2.4	55.7 ± 8.2	50.8 ± 8.7	6.2 ± 1.3	5.5 ± 1.9	2.3 ± 1.1

A AUC_{inf} higher than 20% (24.6%) in comparison to the AUC_{0-24h}. This value should be considered with caution.

Table 2: Concentrations of Gabapentin and Ketoprofen in Brain and Plasma 24 hours Post-Administration via Oral Gavage.

Test Item	Ketoprofen in brain ng/g	Gabapentin in brain ng/g	Ketoprofen in plasma ng/mL	Gabapentin in plasma ng/mL	Brain/Plasma Ratio Ketoprofen %	Brain/Plasma Ratio Gabapentin %
KLS/ Gabapentin co-crystal	633 ± 313	320 ± 173	15046 ± 8590	386 ± 259	4.6 ± 1.7	91.5 ± 18.8

Data clearly demonstrated that gabapentin was able to cross the blood brain barrier, showing a 91.5% of brain:plasma ratio. Interestingly, the brain penetration of ketoprofen was higher compared to the administration of ketoprofen alone (0.92%).

Further details regarding the preclinical data can be found in the Investigator Brochure (IB).

1.3.3. Toxicology

Two studies in minipigs were conducted. In the first minipig study conducted CCI the dose of KLS was mistakenly multiplied by a coefficient factor of 2.25, thus resulting in a 2.25-fold dose increase (22.5 mg/kg/day instead of 10 mg/kg/day), generating an immediate onset of severe clinical signs following the administration of DFL24412.

After analysis of the study procedures and results, it was determined that the dose level that was mistakenly administered to the minipigs corresponded to a human equivalent dose (HED) of 1226 mg KLS. This is 15.3-fold higher than the first single dose proposed in Part A of this study (80 mg KLS).

A second study in minipigs was conducted CCI using the correct dose of KLS combined with gabapentin. The drug combination was administered to two groups of animals, where each group received either a low content of impurity A in gabapentin (0.04%) or a high content of impurity A in gabapentin (3.3%).

Both drug products (with low and high content of impurity A) were well tolerated. There were no mortalities or changes in clinical parameters, with the exception of some haematological changes, including decreased levels of erythrocytes, haemoglobin and haematocrit, and a slight increase of reticulocytes. These values correlated with the minimal or mild erosion/ulceration seen in the stomachs of some animals in both treatment groups.

The changes observed in this study CCI are in line with those induced by NSAIDs in animals. Oral NSAIDs mostly affect the gastrointestinal tract, liver and kidney, inducing changes in these organs when doses are exceeded, or the treatment is prolonged. The minipig is a suitable animal model for extrapolating pharmacological, pharmacokinetics and tolerability data to humans.[23,24] The dose administered makes a fundamental difference in the tolerability of NSAIDs including ketoprofen, and this is true in animals and in humans.[25]

The HED of KLS administered to minipigs over 1 week of continuous oral treatment is 6.8-fold higher than the dose proposed to be administered as a single dose in this clinical study (Part A, 80 mg KLS). The good tolerability at higher exposure in minipigs provides an adequate safety margin for humans, particularly for this drug type (NSAIDs) where we may have adverse effects at a certain threshold dose (the lowest effective dose significantly reduces the risk of serious adverse effects).[25]

In conclusion, the cause of death of the minipigs in study CCI was clearly identified to be due to the excessive dose of KLS. In the second study in minipigs (CCI), the correct dose of DFL24412 was administered and was well tolerated, with only mild macroscopic and microscopic changes observed in the stomach and in some haematology parameters. Therefore, there are no concerns regarding administration of the study drug to healthy volunteers.

Further details regarding the toxicology studies can be found in the IB.

1.4. Clinical Experience

No clinical studies have been conducted to date with the co-crystal of ketoprofen, lysine and gabapentin (DFL24412). Ketoprofen and gabapentin are well known products with well described clinical experience and safety profiles.

Further details regarding the clinical data of ketoprofen and gabapentin can be found in the IB or the SmPC.

1.5. Risk/Benefit Assessment

There is no clinical data for the co-crystal of ketoprofen, lysine and gabapentin (DFL24412). All the existing clinical data refer only to ketoprofen and gabapentin.

Further information about the known and expected benefits and risks and reasonably expected AEs of ketoprofen and gabapentin may be found in the current IB.

The risk assessment of the co-crystal of ketoprofen, lysine and gabapentin (DFL24412) is based on the preclinical and studies with the co-crystal, and the preclinical studies, clinical studies and large marketing experience for ketoprofen and gabapentin conducted to date. Summaries of findings from these studies can be found in the IB. Details of these risks and the proposed strategy to mitigate/monitor these risks are detailed in Table 3.

In this study, safety will be monitored closely both by subjective reporting and by objective means i.e., serial assessments of vital signs, clinical laboratory evaluations data, physical examinations, 12-lead electrocardiogram (ECG) and AE monitoring. In addition, further assessments may be performed as needed according to the Investigator's judgement. This study will be run in a Clinical Research Unit (CRU) with immediate access to hospital facilities for the treatment of medical emergencies. Participants will remain monitored in the clinic for the duration of the study period and will only be discharged from the CRU at the end of the study period if the Investigator deems it safe to do so.

In Part A, if a subject is scheduled to receive a first or second dose of a COVID-19 vaccination within 5 days prior to receiving a dose of investigational medicinal product (IMP), their dosing session will be rescheduled. In Part B, if a subject is scheduled to receive a first or second dose of a COVID-19 vaccination within 7 days prior to capsaicin exposure, their dosing session will be rescheduled.

The vaccine will be considered as a concomitant medication with no interaction that requires advice.

Table 3: Risk/Benefit Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Skin and subcutaneous tissues reactions (including reactions such as toxic epidermal necrolysis [TEN] and Steven-Johnson Syndrome [SJS])	In an analysis of two European and one US database sources to quantify the risks of SJS and TEN associated with widely used NSAIDs in US and Europe, a total of 373 cases who developed SJS or TEN as outpatients and 1720 controls were included in the International Case-Control Study. Of the 373 cases, 112 were exposed to NSAIDs (excluding aspirin).[26]	Subjects with significant skin allergies, pigmentary disorders, or any active dermatological conditions will be excluded. Systematic medical examinations will be performed closely throughout the trial.
Gastrointestinal disturbance (including gastrointestinal bleeding, ulceration, and perforation)	By inhibiting cyclo-oxygenases (COX) non-selectively, NSAIDs block the formation not only of pro-inflammatory, but also important gastroprotective prostaglandins; this pharmacodynamic effect is responsible for the symptomatic gastrointestinal disturbance associated with orally administered NSAIDs.[27]	Subjects with a clinically relevant history of gastrointestinal disorder will be excluded. Safety monitoring will be performed closely throughout the study.
Hypersensitivity	Hypersensitivity to ketoprofen, such as life-threatening asthma, urticarial and angioedema have been reported after ketoprofen treatment.[28]	Subjects with history of severe adverse reactions or allergies, or a history of anaphylactic reactions to prescription medications, non-prescription medications or food will be excluded. Safety monitoring will be performed closely throughout the study.
Acute interstitial nephritis	NSAIDs have been associated with the development of acute kidney injury, including acute interstitial nephritis.[29] In addition, patients with renal impairment, cardiac failure or hepatic cirrhosis may show a reduction in glomerular blood flow, secondary to a reduction in intrarenal vasodilatory prostaglandin synthesis.[30,31]	Subjects with clinically relevant history of endocrine, cardiovascular, gastrointestinal, hepatic, or renal disorders will be excluded. Renal function will be closely monitored throughout the trial.
Cardiovascular thrombotic events	NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction) and stroke, which can be fatal; this risk may increase with duration of use.[32] A study showed that the estimated adjusted relative risk of heart failure associated with NSAIDs was 1.6 (95% confidence interval = 1.2 – 2.1). The relative risk	Subjects with clinically relevant history of endocrine/diabetic and cardiovascular disorders will be excluded. During the entire trial, medical examinations and the collection of vital signs will be systematically performed.

	was greater during the first month of therapy and was independent of treatment indication. The relative risk was even higher (1.9 [1.3 – 2.8]) among patients with prior history of hypertension, diabetes or renal failure in comparison to a rather low incidence (1.3 [0.9 – 1.9]) among individuals without these conditions.[33] Furthermore, NSAIDs are associated with small, but significant, increase in blood pressure in hypertensive patients.[34]	
Jaundice and hepatitis	Prospective studies show that 1% to 2% of patients taking ketoprofen experience at least transient serum aminotransferase elevations. Marked aminotransferase elevations (>3-fold elevated) occur in <1% of patients. Clinically apparent liver injury with jaundice from ketoprofen is very rare and only individual case reports have been published.[35]	Only subjects who have normal range of AST, ALT, GGT and total bilirubin levels at the screening will be included. These laboratory evaluations will be closely monitored throughout the trial. Subjects with a positive result for HBsAg and anti-hepatitis C antibody (anti-HCV) at screening will be excluded. For any subject who meets the hepatic transaminase threshold criteria, a close observation, including monitoring for symptoms and hepatic function will be performed. (See Section 7.5.1.3 and Appendix 4).
COVID-19 vaccination	No data are available on the use of ketoprofen and gabapentin in subjects who have received the COVID-19 vaccine. In Part A, if a subject is scheduled to receive a first or second dose of a COVID-19 vaccination within 5 days prior to receiving a dose of IMP, their dosing session will be rescheduled. In Part B, if a subject is scheduled to receive a first or second dose of a COVID-19 vaccination within 7 days prior to capsaicin exposure, their dosing session will be rescheduled.	The COVID-19 vaccine will be considered as a concomitant medication. All the details of the vaccine administered must be reported in the eCRF in the concomitant medication form. Any symptoms that occur during the study period will be reported in the eCRF. If a subject has COVID-19 symptoms, they will be withdrawn from the study and will be tested for SARS-CoV-2 according to the current UK standard testing.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; COVID-19 = Coronavirus disease 2019; COX = cyclo-oxygenase; eCRF = electronic case report form; GGT = gamma-glutamyl transferase; HBsAg = Hepatitis B surface antigen; IMP = investigational medicinal product; NSAIDs = Non-steroidal anti-inflammatory drugs; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SJS = Steven-Johnson Syndrome; TEN = toxic epidermal necrolysis.

Important identified risks associated with Gabapentin use are:

- Abuse and dependence
- Concomitant use with opioids
- Drug rash with eosinophilia and systemic symptoms (DRESS)
- Drowsiness/dizziness

Important potential risks associated with Gabapentin use are:

- Suicidality
- Pancreatitis

Given the significantly low dose of gabapentin contained in the investigational medicinal product (IMP), the prohibition of taking concomitant drugs and the inclusion of other exclusion criteria, these risks associated with gabapentin use are not expected to occur. However, subjects will be continuously monitored so that immediate action can be taken if necessary.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives (Part A)

2.1.1. Primary Objective

The primary objective of the study is:

- To determine the single dose PK of KLS-GABA (80 mg-34 mg) compared to KLS alone (80 mg) in healthy male subjects.

2.1.2. Secondary Objectives(s)

The secondary objective of the study is:

- To determine the safety and tolerability of a single oral dose of KLS-GABA (80 mg-34 mg) compared to KLS alone (80 mg) in healthy male subjects.

2.2. Objectives (Part B)

2.2.1. Primary Objective

The primary objective of the study is:

- To determine the pharmacodynamic (PD) effects of KLS-GABA in the ID capsaicin model in healthy male subjects.

2.2.2. Secondary Objectives(s)

The secondary objectives of the study are:

- To further investigate the safety, tolerability, and PK of single oral doses of KLS-GABA and KLS alone.
- To investigate the possible relationship between plasma levels of drug and efficacy in pain reduction.

2.3. Endpoints (Part A)

2.3.1. Primary Endpoints

The primary endpoints are plasma PK concentrations and parameters of ketoprofen alone when administered as KLS and ketoprofen and gabapentin when administered as KLS-GABA, including but not limited to: area under the concentration-time curve (AUC), from zero to the last quantifiable concentrations (AUC_{0-t}), AUC from zero to infinity ($AUC_{0-\infty}$), AUC from zero to 12 hours postdose (AUC_{0-12h}), AUC from zero to 24 hours postdose (AUC_{0-24h}), AUC from zero to 36 hours postdose (AUC_{0-36h}), AUC from zero to 48 hours postdose (AUC_{0-48h}), C_{max}, t_{max} and half-life ($t_{1/2}$) in healthy male subjects.

2.3.2. Secondary Endpoints

The secondary endpoint of the study is the clinical safety data from AE reporting, 12-lead ECG, vital signs (supine blood pressure, heart rate, oral temperature), clinical laboratory evaluations (chemistry, haematology, urinalysis and coagulation) and physical examinations in healthy male subjects.

2.4. Endpoints (Part B)

2.4.1. Primary Endpoint

The primary endpoint of the study is:

- Analgesia/reduction in pain post capsaicin injection from the ID capsaicin model.

2.4.2. Secondary Endpoint(s)

The secondary endpoints of the study are:

- Subjective rating of pain from the ID capsaicin model.
- Pain score of hyperalgesia from the ID capsaicin model.
- Area and pain score of brush-evoked allodynia from the ID capsaicin model.
- Area of flare (AF) from the ID capsaicin model.
- Plasma PK concentrations.
- Clinical safety data from AE reporting, 12-lead ECG, vital signs (supine blood pressure, heart rate, oral temperature), clinical laboratory evaluations (chemistry, haematology, urinalysis, and coagulation) and physical examinations in healthy male subjects.

3. STUDY DESIGN

This is a Phase I, randomised, 2-part study to determine the PK, safety, and tolerability of single oral doses of KLS-GABA compared to KLS alone in healthy male subjects (Part A), in addition to investigating the PD effects, PK/PD correlation, safety, and tolerability of three single oral dose levels of KLS-GABA compared to three single oral dose levels of KLS alone, 300 mg gabapentin alone and placebo in the ID capsaicin model in healthy male subjects (Part B).

3.1. Part A

Part A is a randomised, double-blind, crossover group study to investigate a single oral dose of KLS-GABA compared to KLS alone, in healthy male subjects.

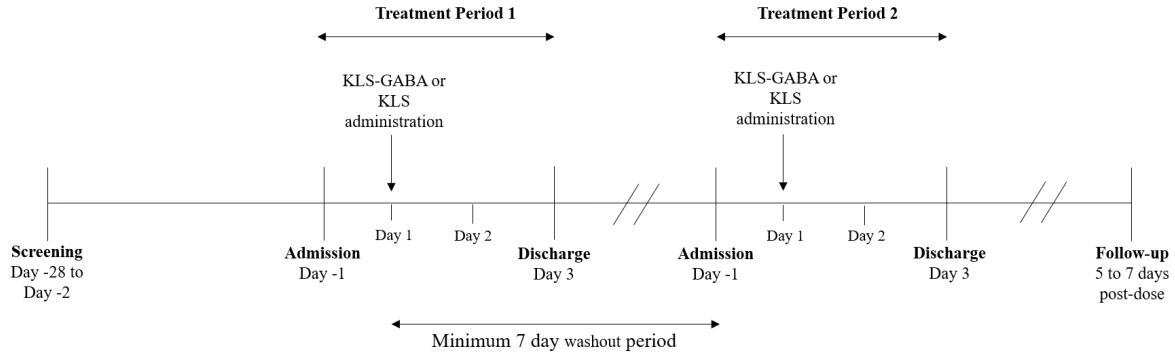

Figure 4: Study Design (Part A)

It is planned to enrol 12 subjects. Subjects will take part in 2 treatment periods, in which they will receive a single dose of KLS-GABA (80 mg-34 mg) or a single dose of KLS (80 mg) alone in each treatment period.

Subjects will be required to attend the CRU for a screening visit up to 28 days prior to first dosing in Treatment Period 1 to ensure they meet the inclusion/exclusion criteria and are in good general health (Section 6).

Subjects will be admitted to the CRU on Day -1 of each treatment period for a body weight assessment and will receive a dose of KLS-GABA or KLS alone in the morning of Day 1. All subjects will undergo predose safety assessments and PK blood sampling on Day 1. All subjects will remain in the CRU until Day 3 (48 hours postdose) for the collection of safety assessments and PK blood samples at multiple time points. There will be a minimum of 7 days washout period between treatment periods.

Subjects will attend a follow-up visit 5 to 7 days post the final dose after Treatment Period 2. The duration of participation for each subject is expected to last approximately 7 weeks. A detailed plan of study assessments is provided in Appendix 1.

3.2. Part B

Part B is a randomised, double-blind, placebo-controlled parallel group study to investigate single oral doses of KLS alone or KLS-GABA compared to 300 mg gabapentin alone or placebo, in healthy male subjects using the ID capsaicin model.

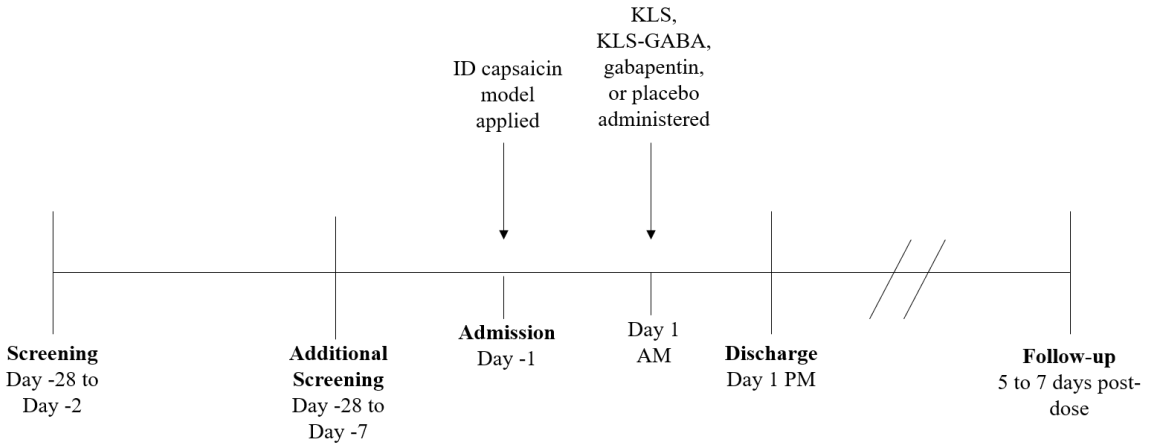

Figure 5: Study Design (Part B)

It is planned to enrol 128 subjects randomised evenly to 8 possible treatments; subjects will receive either KLS alone, KLS-GABA, 300 mg gabapentin or placebo.

The planned treatments are:

- KLS alone (40 mg, 80 mg or 160 mg)
- KLS-GABA (40 mg-17mg, 80 mg-34 mg, or 160 mg-68 mg)
- Gabapentin* (300 mg)
- Placebo

* Product commercialised in Italy: Neurontin 300 mg hard capsules.

Subjects will be required to attend the CRU for a screening visit within 28 days prior to dosing to ensure they meet the inclusion/exclusion criteria and are in good general health (Section 6).

Following initial screening, subjects will be required to attend the CRU for an additional screening visit at least 7 days prior to first dosing to assess their response to capsaicin and familiarise them in the pain measurements. Subjects will receive a single ID administration of 100 µg capsaicin into a novel site on the volar surface of the forearm. Prior to and 15 minutes after administration of capsaicin, measurements of pain, hyperalgesia, allodynia and AF will be performed according to the procedures described in Section 9. In order for the subjects to be eligible, they must be able to tolerate the injection and also demonstrate a sufficient response, defined as an area of hyperalgesia $\geq 15cm^2$ 15 minutes after the injection.

Subjects will be admitted to the CRU on Day -1 for collection of baseline safety assessments, pain measurements and to complete the ID capsaicin model (see Appendix 2). Subjects will receive a single 100 µg capsaicin injection into a novel site on the volar surface of the forearm.

Subjects will receive a single oral dose of KLS alone (40 mg, 80 mg or 160 mg), KLS-GABA (40 mg-17 mg, 80 mg-34 mg or 160 mg-68 mg), 300 mg gabapentin or placebo in the morning of Day 1. All subjects will undergo predose safety assessments, pain measurements and PK blood sampling on Day 1. PK blood samples will also be taken prior to application of the ID capsaicin model on Day 1. All subjects will have an ID capsaicin injection on Day 1 at the t_{max} determined for KLS alone or KLS-GABA from Part A. All subjects will remain in the CRU until 12 hours postdose for the collection of safety assessments, pain measurements and PK blood samples at multiple timepoints.

Subjects will attend a follow-up visit 5 to 7 days postdose. The duration of participation for each subject is expected to last approximately 6 weeks. A detailed plan of study assessments is provided in Appendix 2.

3.3. Rationale for Study Design

This study is designed to evaluate the PK profile, safety, and tolerability of single oral doses of KLS-GABA compared to KLS alone in healthy male subjects (Part A), in addition to investigating the safety, tolerability, PK and PD effects of three single oral dose levels of KLS-GABA compared to three single oral dose levels of KLS alone, 300 mg gabapentin alone and placebo in the ID capsaicin model in healthy male subjects (Part B).

A crossover design will be utilised in Part A to permit a within-subject comparative assessment of the safety and PK of KLS-GABA compared to KLS alone in healthy male subjects. A minimum washout period of 7 days has been selected based on the $t_{1/2}$ of KLS and gabapentin, and therefore should be sufficient to ensure clearance of the drug.

Placebo is included in Part B of the study to permit comparative assessment of the safety and tolerability of KLS alone, KLS-GABA, and gabapentin alone, and to evaluate the balance of benefit and risk of KLS-GABA.

Intradermal injection of capsaicin has been widely used as a challenge agent to induce symptoms of neuropathic pain such as hyperalgesia and allodynia for periods of up to 8 hours post administration. In these challenge studies, capsaicin injection has been shown to be safe, well-tolerated and does not produce any lasting damage to the subjects injected. The use of ID capsaicin provides a safe and scientifically meaningful model to investigate the potential efficacy of drugs for neuropathic pain and other chronic pain conditions.[14]

This study includes standard assessments to evaluate safety and tolerability, including vital signs, physical examinations, 12-lead ECGs, clinical laboratory evaluations and AE collection.

Healthy male subjects have been selected for this study to mitigate any confounding effects of disease state and concomitant medications. Subjects with a skin type compatible with capsaicin measurements have been chosen, and subjects who can tolerate capsaicin injections, have been chosen to participate in Part B to allow collection of pain measurements.

To mitigate the risks to subject and CRU staff safety from the current COVID-19 pandemic, participation in the study will be conditional on respecting local lockdown rules. Government guidelines and local lockdown rules will be respected throughout the duration of the study. MAC and the Sponsor will risk assess any significant changes that may impact on local travel. The subject's ability to travel will be checked during the recruitment process and this information updated at the time of scheduling individual subject's visits.

3.4. Dose Rationale

Ketoprofen and gabapentin, the two individual components of the IMP, are both authorised medicinal products and have been widely used in clinical practice for many years. Therefore, the doses selected for this study are supported by clinical safety data deriving from extensive experience with these drugs.

The labelled doses of KLS are 40 mg up to 3 times per day, or KLS 80 mg up to 2 times per day. The maximum dose of ketoprofen is 200 mg. Gabapentin administration can be administered by titrating the dose (e.g., Day 1: 300 mg once a day; Day 2: 300 mg two times a day; Day3: 300 mg three times a day), or by administering 300 mg three times per day from

Day 1. Based on individual patient response and tolerability, the gabapentin dose level can be further increased in 300 mg/day increments every 2 to 3 days, up to a maximum of 3600 mg/day.

The current study in healthy volunteers is planned to consist of a single oral dose of KLS-GABA (80 mg-34 mg) in Part A, and three oral dose levels of KLS-GABA once daily in Part B, as follows:

- KLS 40 mg/GABA 17 mg,
- KLS 80 mg/GABA 34 mg
- KLS 160 mg/GABA 68 mg

These doses are within the range considered to be safe and with acceptable tolerability in the previous clinical trials investigating both ketoprofen and gabapentin. Further details can be found in the IB or the SmPC.

The selection of dose and dose regimen specifically related to the KLS-GABA co-crystal is based on the currently available non-clinical information. In preclinical models, the co-crystal was proven to be more effective compared to administration of KLS alone, gabapentin alone and coadministration of KLS and gabapentin.

3.5. Individual Stopping Criteria

Any subject who experiences increases in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥5-fold upper limit of normal (ULN), or ≥3-fold ULN with concomitant serum total bilirubin ≥2-fold the ULN and ≥35% direct, will be withdrawn from the study and will be followed until resolution of the abnormal laboratory values.

Subjects will be withdrawn from any further IMP administration if the subject individually fulfils any of the stopping criteria detailed in Section 3.6.

3.6. Study Stopping Criteria

Other stopping criteria will also include:

- A ‘serious’ adverse reaction (see Section 7.5.1.2 for definition of ‘serious’) in 1 subject, i.e., a serious adverse event (SAE) that is considered at least possibly related to IMP administration.
- A ‘severe’ non-serious adverse reaction (i.e., severe non-serious adverse events [AEs] considered as, at least, possibly related to IMP administration) in 2 subjects at the same dose level, independent of within or not within the same System Organ Class (SOC).
- If there is an unacceptable tolerability profile for the IMP based on the nature, frequency and intensity of observed AEs and/or clinical safety monitoring.
- If a subject tests positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

If any of the study stopping criteria are fulfilled, all dosing will be stopped immediately in all study subjects. No further dosing will be permitted at a group or individual level.

If 2 adverse reactions occur that the concern the Investigator and warrant the unblinding of treatment, the study will be halted, and a notification will be sent to the Regulatory Authority to confirm the status of the study and the reason for the study halt. The Investigator has the sole responsibility for determining if unblinding of treatment is necessary for medical management of an event.

If the trial is halted due to safety concerns, or because the stopping criteria are fulfilled, the trial will only resume after Regulatory Authority approval via a substantial Amendment.

4. STUDY SETTING

A single clinical research facility will be used for both parts of this study.

5. STUDY TREATMENTS

5.1. Name and Description of Investigational Product(s)

The KLS, KLS-GABA, gabapentin and placebo will be provided as capsules for oral administration.

Further supportive information will be provided in the Pharmacy Manual.

The KLS-GABA, KLS and placebo IMP will be manufactured to Good Manufacturing Process (GMP) standards and used exclusively in the clinical study according to the instructions in this Protocol and the Pharmacy Manual. The gabapentin will be a commercially available hard capsule (Neurontin) 300 mg. Until the IMP is dispensed to the subjects, it should be stored at a controlled room temperature of 15-25°C.

The Investigator will be responsible for storage and accountability of the IMP. Safety information regarding the IMP is provided in the IB.

5.2. Treatment Administration

5.2.1. Part A

KLS 80 mg capsules or co-crystal KLS-GABA 114 mg (80 mg-34 mg) capsules will be administered once in the morning of Day 1 in Part A in either Treatment Period 1 or 2, according to the randomisation schedule in the fasted state. Capsules will be administered with 240 mL of water.

5.2.2. Part B

The active IMP in Part B (KLS, KLS-GABA, or gabapentin) or placebo will be administered once in the morning of Day 1 as capsules in the fasted state. Subjects assigned to receive 160 mg KLS alone will be administered two KLS 80 mg capsules, and subjects assigned to receive 160 mg-68 mg KLS-GABA will be administered two co-crystal KLS-GABA 114 mg (80 mg-34 mg) capsules. To maintain the blind, subjects assigned to receive either 40 mg KLS alone, 80 mg KLS alone, 40 mg-17mg KLS-GABA, 80 mg-34 mg KLS-GABA or 300 mg gabapentin will also receive a placebo capsule (dummy placebo). Subjects assigned to receive placebo will receive 2 placebo capsules. Capsules will be administered with 240 mL of water.

Subjects will be fasted overnight prior to dosing until 3 hours postdose. Water will be allowed ad libitum except for 1 hour before and 3 hours after dosing.

5.3. Concomitant Medication

The Investigator may review medication use on a case-by-case basis to determine if its use would compromise subject safety or interfere with study procedures or data interpretation (exclusion criteria relating to concomitant medication are presented in Section 6.2). By exception, the subject may take acetaminophen (less or equal 2 g/day) for up to 48 hours prior to dosing. All concomitant medications used (including over-the-counter [OTC] medications and herbal supplements) will be recorded in the source documents and on the appropriate electronic case report form (eCRF).

5.4. Assessment of Compliance with Treatment

All doses will be administered by study staff under direct observation. The administration of the study drug will be recorded within the appropriate pages of the eCRF. Any deviations from the planned dosing procedure will be recorded within the eCRF.

5.5. Blinding

This study will be double-blinded (Investigator- and subject-blinded). The randomisation list will be kept in a secure location until the end of the study. Only the Pharmacy staff involved in handling the study drug, an unblinded dosing team, and laboratory staff responsible for analysing the PK blood samples will be unblinded during the study and will have access to the randomisation list. The laboratory responsible for analysing the PK blood samples will maintain the blind of other individuals involved in the study and will share the draft analytical results in a codified manner, according to the Dompé SOP, to maintain the blind.

The Investigator has complete autonomy over participant safety throughout the duration of the study and will have access to the code break envelopes to ensure he/she is able to unblind any of the study participants only in the case of medical emergency. EUDRAC Ltd (and Dompé Pharmacovigilance) are unblinded for this study and will have access to the code-break envelopes for the purposes of carrying out safety related regulatory submissions and also as emergency cover should this be necessary.

5.6. Emergency Unblinding

The study blind should not be broken except in a medical emergency where knowledge of the treatment identity is essential for treating the subject. The Investigator has the sole responsibility for determining if unblinding of treatment is necessary for medical management of an event. If the treatment blind needs to be broken in the interest of patient safety in the event of a medical emergency, the Investigator is allowed to break the treatment code for the specific patient, even before informing the Sponsor. To ensure the ongoing monitoring of the benefit-risk profile of the IMP, the Investigator must always notify the Sponsor of any emergency unblinding due to medical reasons, so that the reason for any premature unmasking can be documented. This will be done by means of a communication to EUDRAC and secondary to Dompé. Unblinding is performed through the use of Code Break materials. The Code Break materials are secured in the pharmacy safe with the safe code readily accessible by the Investigator if there is an emergency. The applicable SOPs will be followed to break the blind.

Dompé Pharmacovigilance Department is allowed to unblind treatment only for documented safety reasons, and before regulatory reporting of a potential Suspected Unexpected Serious Adverse Reaction (SUSAR), to fulfil expedited regulatory reporting requirements.

Unblinded information shall not be disclosed to the Investigator, Medical Monitor and the Sponsor’s Clinical Development Department.

After database lock, the overall randomisation code will be broken only for reporting purposes.

6. SELECTION AND WITHDRAWAL OF SUBJECTS

The study population includes 12 healthy male subjects in Part A and 128 healthy male subjects in Part B. Each subject should meet all the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

6.1. Inclusion Criteria

6.1.1. Part A

Subjects meeting the following criteria will be included in the study:

1. Subject is male, of any ethnic origin.
2. Subject is aged between 18 to 55 years, inclusive.
3. Subject has a body mass index (BMI) of 18 to 32 kg/m^2, inclusive.
4. Subject is ≥50 kg.
5. Negative SARS-CoV-2 test at Screening and Day -1 in each treatment period.
6. Healthy as determined by a responsible physician, based on medical evaluation including medical history, physical examinations, concomitant medication, vital signs, 12-lead ECG, and clinical laboratory evaluations.
7. Subjects must use a condom during the trial and for 3 months after their final dose of trial medication, if their partner is a woman of childbearing potential. In addition, their female partner of childbearing potential must use an additional method of highly effective contraception (see Section 6.4.1) from dosing until 3 months following dosing.
8. Subject is either a non-smoker or does not smoke more than 5 cigarettes per day (or equivalent e-cigarette use).
9. Provision of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.

6.1.2. Part B

Subjects meeting the following criteria will be included in the study:

1. Subject is male, with a skin type compatible with capsaicin measurements.
2. Subject is aged between 18 to 55 years, inclusive.
3. Subject has a BMI of 18 to 32 kg/m^2, inclusive.
4. Subject is ≥50 kg.
5. Negative SARS-CoV-2 test at Screening and Day -1.
6. Healthy as determined by a responsible physician, based on medical evaluation including medical history, physical examination, concomitant medication, vital signs, 12-lead ECG, and clinical laboratory evaluations.

7. Subject must be in good general health with a skin type compatible with the measures, and without significant skin allergies, pigmentary disorders, or any active dermatological conditions that might interfere with the conduct of the study.
8. Subjects must use a condom during the trial and for 3 months after their final dose of trial medication, if their partner is a woman of childbearing potential. In addition, their female partner of childbearing potential must use an additional method of highly effective contraception (see Section 6.4.1) from dosing until 3 months following dosing.
9. Subjects must be able to tolerate the capsaicin injection at screening.
10. Demonstration of positive hyperalgesia as defined by an area of hyperalgesia ≥15 cm^2 15 minutes after ID administration of 100 µg capsaicin at the additional screening visit at least 7 days prior to first dosing.
11. Subject is a either non-smoker or does not smoke more than 5 cigarettes per day (or equivalent e-cigarette use).
12. Provision of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.

6.2. Exclusion Criteria (Part A)

Subjects with any of the following will be excluded from study participation:

1. Clinically relevant history of abnormal physical or mental health interfering with the study as determined by medical history and physical examinations obtained during screening as judged by the Investigator (including [but not limited to], neurological, psychiatric, endocrine/diabetic, cardiovascular, respiratory, gastrointestinal, hepatic, or renal disorder).
2. Clinically relevant abnormal laboratory results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis), 12-lead ECG and vital signs, or physical findings at screening. In case of uncertain or questionable results, tests performed during screening may be repeated once to confirm eligibility or judged to be clinically irrelevant for healthy subjects.
3. History or clinical evidence of any disease and/or existence of any surgical or medical condition which might interfere with the absorption, distribution, metabolism and excretion (ADME) of the study drugs.
4. Any other concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study as outlined in this Protocol, safety of the subject as per the SmPC of KLS and gabapentin (Neurontin 300 mg hard capsules) or that would, in the opinion of the Investigator, pose an unacceptable risk to the subject in this study.
5. Subject has a history of neurological disorders which may impact the perception of pain or impairs the subject's ability to fully participate in the study.
6. Subject has a significant skin allergy, pigmentary disorder, or any active dermatological condition.

7. AST, ALT, gamma-glutamyl transferase (GGT) or total bilirubin levels above the ULN at screening. These laboratory evaluations may be repeated once at the discretion of the Investigator. If the repeat test is within the reference range, the subject may be included only if the Investigator considers that the previous finding will not introduce additional risk factors and will not interfere with interpretation of safety data.
8. Positive test for hepatitis B surface antigen (HBsAg), anti-hepatitis C antibody (anti-HCV) or human immunodeficiency virus I and II antibodies (anti-HIV I/II) at screening.
9. Positive urine test for drugs of abuse or alcohol breath test at screening or Day -1 of each treatment period.
10. History of drug and/or alcohol abuse/dependence, or intake of >28 units of alcohol weekly, and the inability to refrain from alcohol use from 48 hours before screening and each scheduled visit until discharge from the CRU. One unit is equivalent to a 285 mL glass of full-strength beer or 1 (30 mL) measure of spirits or 1 glass (100 mL) of wine.
11. Habitual and heavy consumption of caffeinated beverages (>8 cups of coffee or equivalent per day) at screening; and/or unable to refrain from use of (methyl) xanthine (e.g., coffee, tea, cola, chocolate) from 48 hours prior to dosing until discharge from the CRU.
12. The subject has participated in a clinical study and has received a medication or a new chemical entity within 3 months or 5 half-lives (whichever is longer) prior to dosing of current study medication.
13. Use of any prescription or non-prescription medications, including herbal and nutritional supplements (including St. John's wort), or OTC medications (e.g., ibuprofen, aspirin) within 14 days of dosing and throughout the study. By exception, the subject may take acetaminophen (less or equal 2 g/day) for up to 48 hours prior to dosing. The Investigator may review medication on a case-by-case basis to determine if its use would compromise subject safety or interfere with study procedures or data interpretation.
14. History of severe adverse reactions or allergies, or history of an anaphylactic reaction to prescription medications, non-prescription medication, food, NSAIDs or gabapentin (non-active hay-fever is acceptable).
15. Consumption of any food or drinks containing cranberry, pomegranate, starfruit, grapefruit, pomelos, exotic citrus fruits or Seville oranges (including marmalade and juices made from these fruits) within 14 days before admission to the CRU until the end of the study.
16. Strenuous exercise within 48 hours prior to each blood collection for clinical laboratory tests.
17. Donation of blood or plasma of >500 mL within 3 months prior to first dosing, or subject intends to donate blood during the study.
18. Male subject who will not abstain from sperm donation between dosing and 3 months after final dosing.

19. Any degree of previous or known hypersensitivity to the active substance or the excipients of the IMP.

6.3. Exclusion Criteria (Part B)

Subjects with any of the following will be excluded from study participation:

1. Clinically relevant history of abnormal physical or mental health interfering with the study as determined by medical history and physical examinations obtained during screening as judged by the Investigator (including [but not limited to], neurological, psychiatric, endocrine/diabetic, cardiovascular, respiratory, gastrointestinal, hepatic, or renal disorder).
2. Clinically relevant abnormal laboratory results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis), 12-lead ECG and vital signs, or physical findings at screening. In case of uncertain or questionable results, tests performed during screening may be repeated once to confirm eligibility or judged to be clinically irrelevant for healthy subjects.
3. Has a skin trauma, any active skin disorder, significant scarring, significant skin allergy, pigmentary disorder, active dermatological condition, skin disease or tattoos on either forearm, or a significant history of trauma or skin disease in either arm.
4. Subject has a known intolerance to capsaicin, hot peppers, or any excipient in the IMP.
5. Subject has active chronic pain condition(s) or a history of chronic pain conditions.
6. History or clinical evidence of any disease and/or existence of any surgical or medical condition which might interfere with the ADME of the study drug.
7. Any other concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study as outlined in this Protocol, safety of the subject as per the SmPCs of KLS and gabapentin (Neurontin 300 mg hard capsules) or that would, in the opinion of the Investigator, pose an unacceptable risk to the subject in this study.
8. Subject has a history of neurological disorders which may impact the perception of pain or impairs the subject's ability to fully participate in the study.
9. AST, ALT, GGT or total bilirubin levels above the ULN at screening. These laboratory evaluations may be repeated once at the discretion of the Investigator. If the repeat test is within the reference range, the subject may be included only if the Investigator considers that the previous finding will not introduce additional risk factors and will not interfere with interpretation of safety data.
10. Positive test for HBsAg, anti-HCV or anti-HIV I/II at screening.
11. Positive urine test for drugs of abuse or alcohol breath test at screening.
12. History of drug and/or alcohol abuse/dependence, or intake of >28 units of alcohol weekly, and the inability to refrain from alcohol use from 48 hours before Screening and each scheduled visit until discharge from the CRU. One unit is equivalent to a 285 mL glass of full-strength beer or 1 (30 mL) measure of spirits or 1 glass (100 mL) of wine.

13. Habitual and heavy consumption of caffeinated beverages (>8 cups of coffee or equivalent per day) at screening; and/or unable to refrain from use of (methyl) xanthine (e.g., coffee, tea, cola, chocolate) from 48 hours prior to dosing until discharge from the CRU.
14. The subject has participated in a clinical study and has received a medication or a new chemical entity within 3 months or 5 half-lives (whichever is longer) prior to dosing of current study medication.
15. Use of any prescription or non-prescription medications, including herbal and nutritional supplements (including St. John's wort), or OTC medications (e.g., ibuprofen, aspirin) within 14 days of dosing and throughout the study. By exception, the subject may take acetaminophen (less or equal 2 g/day) for up to 48 hours prior to dosing. The Investigator may review medication on a case-by-case basis to determine if its use would compromise subject safety or interfere with study procedures or data interpretation.
16. History of severe adverse reactions or allergies, or history of an anaphylactic reaction to prescription medication, non-prescription medication, food, NSAIDs, gabapentin, (non-active hay-fever is acceptable), the planned local anaesthesia/analgesic regimens, ethylenediaminetetraacetic acid, Kolliphor HS 15, butylated hydroxytoluene, or capsaicin.
17. Known hypersensitivity or allergy to any component of the placebo capsules.
18. Consumption of any food or drinks containing cranberry, pomegranate, starfruit, grapefruit, pomelos, exotic citrus fruits, or Seville oranges (including marmalade and juices made from these fruits) within 14 days before admission to the CRU until the end of the study.
19. Strenuous exercise within 48 hours prior to each blood collection for clinical laboratory tests.
20. Subject has participated in a clinical study involving administration of capsaicin within 12 months of the screening visit.
21. Donation of blood or plasma of >500 mL within 3 months prior to dosing, or subject intends to donate blood during the study.
22. Male subject who will not abstain from sperm donation between dosing and 3 months after dosing.
23. Any degree of previous or known hypersensitivity to the active substance or the excipients of the IMP.

6.4. Study Restrictions

6.4.1. Contraception Restrictions

Male subjects with a female sexual partner of child-bearing potential must wear a condom (from first dosing until 3 months after final dosing) in addition to their female partner using a highly effective method of contraception, from first dosing until 3 months following final dosing. Contraceptive methods that can achieve a failure rate of less than 1% per year when

used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device or intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Surgical sterilisation

If the male subject is vasectomised then this will be accepted as a second form of highly effective contraception, in addition to the subject also wearing a condom. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatment and must be part of the preferred and usual lifestyle of the subject.

6.4.2. Lifestyle Restrictions

Subjects should abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests, and while in the CRU.

Subjects participating in Part B of the study must refrain from sunbathing during their participation in the study (from Screening to discharge from the CRU following completion of all procedures).

6.4.3. Meals and Dietary Restrictions

The subjects are required to adhere to the following restrictions:

- Subjects should refrain from consumption any food or drinks containing cranberry, pomegranate, starfruit, grapefruit, pomelos, exotic citrus fruits, or Seville oranges (including marmalade and juices made from these fruits) within 14 days before admission and throughout the study until completion of study.
- Subjects should abstain from alcohol for 48 hours prior to each visit until after discharge from the CRU.
- Subjects should abstain from (methyl) xanthine- and caffeine-containing products for 48 hours prior to dosing until discharge from the unit from CRU.

- Subjects will be fasted overnight for at least 8 hours predose until 3 hours postdose. In addition, subjects should fast 4 hours prior to clinical laboratory evaluations at each visit. Water will be allowed ad libitum, except for 1 hour before and 3 hours after dosing. Standard meals and drinks will be provided at all other times.
- Subjects should refrain from consuming poppy seeds 48 hours prior to Screening and Day -1 (in each treatment period for Part A) to avoid a positive result on the drugs of abuse screen.

6.5. Subject Withdrawal Criteria

For all subjects withdrawn from the study, discontinuation procedures as described in Appendix 1 and Appendix 2 should be conducted prior to discharge in the study. In Part B, subjects will be replaced should they vomit after receiving their dose of IMP, or if they do not receive the ID capsaicin.

Reasons for withdrawal or discontinuation at any time during the study may include any of the following reasons:

- Adverse event: Clinical or para-clinical events occurred that, in the medical judgement of the Investigator for the best interest of the subjects, are grounds for discontinuation. This includes serious and non-serious AEs regardless of relation to the study medication.
- Withdrawal of consent: The subject desired to withdraw from further participation in the study in the absence of an Investigator determined medical need to withdraw. If the subject gave a reason for withdrawing it should be recorded in the eCRF.
- Investigator decision.
- Lost to follow-up: The subject stopped coming for visits and study personnel were unable to contact the subject.
- The subject tests positive for SARS-CoV-2 at any point during the study.
- Other: The subject was discontinued for a reason other than those listed above, such as termination of the study by the Sponsor. The reason(s) should be recorded in the eCRF.

6.6. Follow-up Procedures

The Investigator will make diligent attempts to contact subjects who fail to return for a scheduled visit or were otherwise unable to attend the follow-up visit. All discontinuations and the reason for early discontinuation will be documented by the Investigator, and if appropriate on the AE form.

7. SAFETY ASSESSMENTS

Baseline safety data assessments for all parts of the study will be collected predose at the nearest timepoint to dosing as shown in Appendix 1 and Appendix 2. The subjects will attend a follow-up visit 5 to 7 days post-discharge from the CRU for safety follow-up procedures as shown in the Schedule of Assessments (Appendix 1 and Appendix 2).

7.1. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed including [clinical chemistry, haematology, coagulation, and urinalysis] as indicated in the table below (Table 4). Serology, drugs of abuse, alcohol and SARS-CoV-2 (according to the current UK standard testing) screen will be performed as indicated in the table below (Table 4). Approximate blood sampling volumes are provided in Appendix 3.

All blood and urine analyses will be conducted at the sampling times indicated in the Schedule of Assessments (Appendix 1 and Appendix 2). The clinical laboratory evaluation results will be collected at screening (in Part A and B) and at check-in on Day -1 to the CRU (in Part B), in time for results to be reviewed prior to dose administration. For abnormal values, additional testing may be performed, or clinical laboratory evaluations may be added to evaluate the abnormal values. Clinically significant values should be followed until resolution or until they reach a stable state.

Table 4: Clinical Laboratory Evaluations

Blood Chemistry Amylase BUN Creatinine Glucose Sodium Potassium Phosphate Chloride Calcium AST ALT GGT Alkaline phosphatase Total bilirubin Uric acid Albumin Total protein Lactate dehydrogenase	**Urinalysis (dipstick)** Glucose Bilirubin Ketone Specific Gravity Blood pH Protein Urobilinogen Nitrite Leukocyte Esterase Microscopic analysis if dipstick is abnormal
Haematology Haemoglobin Haematocrit RBC count RBC indices (MCV, MCH, MCHC) Platelet count White blood cell count with differential	**Drugs of abuse** Amphetamines Barbiturates Benzodiazepines Cocaine Cannabinoids Opiates
Coagulation Prothrombin time International normalization ratio Activated partial thromboplastin time	**Other Screens** Alcohol (breath) SARS-CoV-2 according to the current UK standard testing

	Virology Anti-HIV I/II Anti-HCV HBsAg

Abbreviations: ALT – alanine aminotransferase; Anti-HIV I/II – Anti-human immunodeficiency virus I and II; Anti-HCV – anti-hepatitis C antibody; AST: aspartate aminotransferase; BUN – blood urea nitrogen; GGT – gamma-glutamyltransferase; HBsAG – hepatitis B surface antigen; MCV – mean corpuscular volume; MCH - mean corpuscular haemoglobin; MCHC – mean corpuscular haemoglobin concentration; SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2.

7.2. 12-lead Electrocardiogram

A 12-lead ECG will be collected at the timepoints indicated in the Schedule of Assessments (Appendix 1 and Appendix 2). The 12-lead ECG will be collected in triplicate, approximately 1 minute apart, at Screening, and within approximately 1-hour predose. Single readings will be collected at all other timepoints. 12-lead ECGs should be obtained after the subject has rested in the supine position for at least 5 minutes. In the event of an abnormal finding, recordings should be performed in triplicate. Triplicate recordings will be performed within 30 minutes of an abnormal finding. The ECG machine used should automatically calculate the HR and PR, RR, QRS and QTcF intervals.

For timepoints with multiple assessments:

- collect the ECG first,
- then vital signs,
- then the PK blood draw. The PK sample should be collected at the scheduled time postdose.

7.3. Vital Signs and Oral Temperature

Supine vital signs, including heart rate, blood pressure and oral temperature will be collected at the timepoints in the Schedule of Assessments (Appendix 1 and Appendix 2). Predose vital signs should be collected within 30 minutes predose.

For timepoints with multiple assessments:

- collect the ECG first,
- then vital signs,
- then the PK blood draw. The PK sample should be collected at the scheduled time postdose.

7.4. Physical Examinations

A physical examination, including height, BMI, and body weight, and assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular system, abdomen (liver and spleen), lymph nodes and extremities will be conducted at the times indicated in the Schedule of Assessments (Appendix 1 and Appendix 2).

7.5. Adverse Event Reporting

Adverse event monitoring will be conducted at the times specified in the Schedule of Assessments (Appendix 1 and Appendix 2). Adverse events will be elicited through non-

leading questions and spontaneous reporting by subjects. The Investigator is responsible for evaluating AEs and for the appropriate medical care of subjects during the study.

7.5.1. Definition and Criteria

7.5.1.1. Adverse Event

An AE is any untoward medical occurrence in a study subject which either emerges, or worsens from Screening, during the clinical study, regardless of its potential relationship to the medicinal product. An AE, therefore, can be any unfavourable or unintended sign, including a clinically-significant abnormal laboratory finding, symptom, or disease temporally associated with the use of a medical product, whether or not it is considered to be study medication related.

Examples of an AE include:

- Exacerbation of a pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed.
- Signs or symptoms of a drug interaction.
- Signs or symptoms of a suspected overdose of either IMP or a concurrent medication (overdose per se should not be reported as an AE/SAE)
- A new laboratory abnormality occurring after the start of the study (i.e., after Screening) that results in subject withdrawal from the study or medical treatment or further follow-up.
    - Note: abnormal laboratory or other values obtained during Screening that preclude a subject from entering the study are not considered AEs but will be recorded.

Adverse events may include pre- or post-treatment events that occur as a result of Protocol- mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen).

A medical intervention to address an AE is an "action taken" and not an AE itself.

7.5.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death,
- Is life-threatening,
    - Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires hospitalisation or prolongation of existing hospitalisation,
    - Note: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the

physician's office or out setting. Complications that occur during hospitalisation are AEs. If complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

- Results in persistent or significant disability or incapacity,
    - Note: The term 'disability' means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital abnormality or birth defect,
- Is an important medical event.
    - Note: Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening, or result in death or hospitalisation, but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.
    - Note: The terms "serious" and "severe" ARE NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is NOT the same as "serious", which is based on subject/event outcome or action criteria described above and are usually associated with events that pose a threat to a subject's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.5.1.3. Suspected Unexpected Serious Adverse Reactions (SUSARs)

A SUSAR is defined as an AE that occurs in a clinical trial subject, which is assessed by the Sponsor and or study Investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study drug. The Sponsor is responsible for the regulatory reporting of SUSARs. An AE will be considered unexpected if the nature, severity, frequency of the event is not consistent with the risk information previously described for the IMPs, and reported in the IB for the study product KLS-GABA (Reference Safety Information [RSI] Section) or in the SmPCs for the medicinal product KLS and gabapentin (Neurontin 300 mg hard capsules), respectively. The process for recording and reporting SUSARs is defined in the Sponsor SOPs in accordance with regulatory guidelines.

7.5.1.4. Expectedness

An AE is considered expected if it is either listed in the IB for KLS-GABA (RSI Section) or the SmPCs for KLS and gabapentin (Neurontin 300 mg hard capsules). An event is unexpected when it is not listed in the IB for KLS-GABA or the SmPCs for KLS and gabapentin (Neurontin 300 mg hard capsules), including when it is not listed at the specificity or severity that has been observed and reported in the IB or SmPCs. Events that are mentioned in the IB or SmPCs as occurring with a class of drugs, or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular IMP, are considered unexpected.

The determination of expectedness shall be made by the Sponsor on the basis of the IB for KLS-GABA RSI Section, or the SmPC for KLS or gabapentin (Neurontin 300 mg hard capsules).

7.5.1.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events and Serious Adverse Events

Abnormal laboratory findings (e.g., clinical chemistry and haematology) or other abnormal assessments (e.g., ECGs, vital signs) that are judged by the Investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. Liver chemistry thresholds have been designed to assure subject safety. When subjects meet the hepatic transaminase threshold criteria (AST or ALT ≥3 x ULN), the subject should undergo close observation, including monitoring for symptoms (clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash) and hepatic function (AST, ALT, alkaline phosphatase [ALP]), and fractionated bilirubin at least every 48 hours, until symptoms and/or hepatic function abnormalities resolve, stabilise, or return to baseline values. This event should be reported to Dompé within 24 hours of learning of its occurrence. Appendix 4 represents the decision tree for whether or not study medication will be discontinued. A specialist or hepatology consultation should be considered in cases of protocol-mandated study medication discontinuation.

In addition, every attempt should be made to obtain the following for any subject who meets the hepatic transaminase threshold criteria:

- Viral hepatitis including: hepatitis A immunoglobulin (IgM) antibody, hepatitis B surface antigen and hepatitis B core antibody (IgM), HCV RNA, cytomegalovirus IgM antibody, Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophil antibody or monospot testing), and hepatitis E antibody (if subject resides outside UK or has travelled outside UK in past 3 months).

- Serum creatine phosphokinase and lactate dehydrogenase. Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form.

- Record use of concomitant medications, including paracetamol, herbal remedies, other OTC medications, putative hepatotoxins, or alcohol on the concomitant medications report form.
- The following are required for subjects with AST or ALT ≥3 x ULN and bilirubin ≥2 x ULN, but are optional for other abnormal liver chemistries:
    - Anti-nuclear antibody, anti-smooth muscle antibody, and type 1 anti-liver kidney microsomal antibodies.
    - Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

7.5.1.6. Pharmacokinetic Sampling Associated with Serious Adverse Events or Severe Adverse Events

Every possible attempt will be made to collect an unscheduled PK sample if a subject experiences an SAE or a severe AE. As the determination of an SAE or a severe AE is sometimes retrospective, unscheduled PK samples obtained when an event that is suspected to be serious or severe are also permitted.

7.5.2. Evaluating Adverse Events and Serious Adverse Events

All AEs will be assessed on two descriptive parameters: intensity and relationship to the study medication:

- Intensity refers to the severity of an event and references impact on a subject's functioning.
- Relationship refers to the likelihood that the event being assessed was caused by the study medication.

The intensity of each AE (including SAEs) will be recorded in the eCRF and assigned to one of the following categories:

- **Mild:** An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe:** An event that prevents normal everyday activities.

For AEs and SAEs, the relationship to the study treatment is to be assessed according to the following definitions:

Not related: There is no reasonable association between the study treatment and the suspected event.

Unlikely related: It is doubtful that there is an association between the study treatment and the suspected event. The event could have been produced by the subject's clinical state or other modes of therapy administered to the subject.

Possibly related: The suspected adverse event may or may not follow a reasonable temporal sequence from study drug administration. The event could have been produced or mimicked

by the subject's clinical state or by other modes of therapy concomitantly administered to the subject.

Probably related: The suspected adverse event follows a reasonable temporal sequence from study treatment administration, abates upon discontinuation of the treatment; and cannot be reasonably explained by the known characteristics of the subject's clinical state.

Definitely related: The suspected adverse event has a strong relationship with study treatment administration, the event abates upon discontinuation of treatment and, if applicable, re-appears upon repeat exposure.

When assessing the relationship to the study medication, the following criteria will be considered:

- Known class effect
- Biological plausibility
- Lack of alternative explanation – concomitant drug or disease

7.5.3. Reporting Procedures and Requirements

7.5.3.1. Adverse Events

Events occurring from the time of signed informed consent will be considered as AEs. A baseline AE assessment will occur after Screening. All AEs between screening to the follow- up visit will be recorded in source and eCRF, whether or not considered study medication related. All AEs that are possibly or probably related to study medication will be followed until resolution or database lock, whichever occurs first. Also, the sign, symptom, or disease present before the baseline AE assessment are only considered AEs if they worsen after this point. Any AEs already documented at a previous assessment and designated as ongoing should be reviewed at subsequent visits as necessary. If these have resolved, this should be documented. Changes in intensity or frequency of AEs should be recorded as separate events (i.e., a new record started). The Investigator should report all AEs on the AE page(s) of the eCRF and source documents, regardless of seriousness, severity, and causality. Whenever possible, an AE will be reported using a diagnostic term, (e.g., "common cold" or "upper respiratory infection" rather than "runny nose, cough, mild fever") and should be described with the attributes described in Section 7.5.1.1.

7.5.3.2. Serious Adverse Events

Each AE will be assessed to determine whether it meets seriousness criteria (Section 7.5.1.2). If the AE is considered serious the Investigator should report this event to the Sponsor. The Investigator shall also promptly report an SAE with a fatal outcome to the research ethics committee (REC). Serious adverse events occurring from the time of signed informed consent to the follow-up visit or 7 days after the last dose of study medication (whichever occurs later) will be recorded in source and electronic data capture; ongoing SAEs after this time frame will be followed until the Investigator, Medical Monitor, and Sponsor agree that the SAE is satisfactorily resolved, or stably unresolved.

Serious adverse events considered by the Investigator to be related to study medication, regardless of the time of onset after treatment, should be reported. All information about SAEs will be collected and reported via the SAE form and sent by email message (contact information

will be contained in the Investigator site file). The Investigator should send the initial report within 24 hours of becoming aware of the SAE.

At a minimum, the initial report should include the following information:

- Event
- Seriousness criteria
- Protocol number
- Subject number, initials, and age
- Study medication
- Reporter name and contact information
- Relationship assessment

In the case of a "minimum report" (one that solely comprises the information bulleted above), a more detailed follow-up report should be sent as soon as more information becomes available but no later than 3 calendar days after the date of the initial report.

Each SAE should be followed up until resolution or stabilisation and for reported deaths, the Investigator should supply Sponsor and the REC with any additional requested information (e.g., autopsy reports and terminal medical reports), if available. The original SAE form should be kept at the study site. The Investigator will be responsible for determining and in turn, reporting SAEs to the Sponsor.

7.5.4. Conditions That Should Not be Reported as SAEs

Any condition assessed by the Investigator as serious shall be recorded and reported to the Sponsor as an SAE.

7.5.5. Adverse Events Exemption

Not applicable. All AEs will be recorded in the eCRF by the Investigator and reported as described in this Protocol.

7.5.6. Prompt Reporting of Serious Adverse Events

Any SAE, occurring in a subject receiving treatment or if the Investigator becomes aware of any SAE post-treatment during the follow-up visit, should be reported by the Investigator via email to the Dompé Pharmacovigilance Department, Medical Monitor and EUDRAC Ltd within 24 hours even if the SAE does not appear to be medication-related.

The Investigator shall email a copy of the SAE form, in addition to other related information. Additionally, it may be necessary for the Medical Monitor or Sponsor to directly communicate with the Investigator if additional information is required.

All additional follow-up evaluations should be reported to the Sponsor. Such data should be emailed to the Dompé Pharmacovigilance Department, Medical Monitor and EUDRAC Ltd within 24 hours.

In line with CT3 Detailed Guidance and ICH E2A provisions, although the Investigator does not usually need to actively monitor subjects for AEs once the trial has ended, if the Investigator becomes aware of an SAE occurring in a subject after that subject has ended his participation

in the study (whether study completion or withdrawal), the SAE should be reported by the Investigator to the Dompé Pharmacovigilance Department. Such "post-study cases" should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

A list of expected serious adverse reactions reported in patients treated with ketoprofen or gabapentin as single substances are provided in the IB.

7.5.7. Regulatory Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

During the course of the clinical trial, the Sponsor shall report any SUSAR to the concerned REC and regulatory authority, as soon as possible and in no event later than:

1. 7 calendar days after becoming aware of the information if the event is fatal or life threatening; to be followed by any relevant information within 8 calendar days.
2. 15 calendar days after becoming aware of the information if the event is neither fatal nor life threatening.

The Sponsor will be responsible for completing the safety report and for notifying the relevant authorities of any SAE as outlined in the ICH Guidelines and per local regulatory requirements.

Treatment will be unblinded by the Sponsor's Pharmacovigilance Department prior to regulatory submission of a SUSAR to regulatory authorities and the REC, and only cases referred to active treatment will be considered suitable for expedition for regulatory reporting, in line with law requirements.

Follow up information shall be reported within the same timeframes.

If the results of an investigation show that an adverse drug reaction, not initially determined to be reportable, is reclassified as reportable, the Sponsor shall report such reaction in a written safety report as soon as possible, but in no event later than 7 or 15 calendar days (whichever is applicable) after the determination is made.

In addition, each Investigator will receive appropriate periodical safety updates as per local requirements and regulations.

The Sponsor shall be responsible to prepare and submit annual safety reports (Development Safety Update Report) to relevant regulatory authorities.

7.5.8. Special Considerations

7.5.8.1. Pregnancy of Female Partner of Male Subject

If the female partner of a male subjects becomes pregnant between dosing and 3 months after dosing, the Investigator should report pregnancy within 24 hours after learning of the pregnancy. The Investigator should contact the designated individual(s) following the SAE notification process and record information related to the pregnancy on the designated pregnancy form provided by Dompé or its designee. Early discontinuation visit assessments are required as soon as possible after learning of the pregnancy. The Investigator is also responsible for following any pregnancy following admission until delivery or termination if possible. These findings should be reported on the pregnancy form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous

abortion, congenital anomaly, or reports of suspected adverse reactions in the neonate that are classified as serious.

7.5.8.2. Overdose (if Appropriate)

Cases of overdose (accidental or intentional) which may or may not result in serious adverse reactions are to be reported to the Sponsor Pharmacovigilance Department and the Medical Expert following the same procedure for SAE, within 24 hours from the Investigator's knowledge of its occurrence. This includes reports related to drug intake through different routes (e.g., ingestion) or with suicidal intentions and consequent drug overdose.

In this study, an overdose is defined as the administration of a double dose or more, on any given treatment day.

The Investigator shall provide, in the SAE form, information about symptoms, corrective treatment and outcome of overdose. The Medical Expert should be contacted to discuss corrective treatment, if necessary.

7.6. Other Assessments

Assessments to be performed at Screening only and Day -1 only are detailed in the Schedule of Assessments (Appendix 1 and Appendix 2).

8. PHARMACOKINETIC ASSESSMENTS

8.1. Pharmacokinetic Sampling

Baseline PK blood samples will be collected within 15 minutes predose on Day 1.

Blood samples for determination of plasma concentrations of ketoprofen and gabapentin when administered alone or in combination will be taken at the timepoints stated in Appendix 1 and Appendix 2.

The actual times of collection will be recorded.

Plasma concentration-time data will be analysed by noncompartmental methods. Nominal times may be used for interim decisions, however actual sampling times will be used for final calculations.

8.2. Storage and Analysis of Clinical Samples

Approximate sampling volumes are provided in Appendix 3. Samples will be collected, labelled, stored, and shipped on dry ice as detailed in the Sample Handling Sheets.

Pharmacokinetic blood samples will be collected in polypropylene tubes containing Li-Heparin as anticoagulant, and they will be centrifuged at 4° C for 10 minutes at 2500 g to obtain plasma. Each plasma sample will be immediately divided into two aliquots and stored frozen at -20° C until shipment to the analytical laboratory. The samples will be analysed to quantify ketoprofen and gabapentin using a validated analytical method. The analysis will be performed at Dompé analytical laboratories in L'Aquila (Italy).

Further details will be provided in a standalone document.

9. PHARMACODYNAMIC ASSESSMENTS

9.1. Evaluation of Response to ID Capsaicin

The response to ID injection of capsaicin will be assessed in 6 ways; subjective rating of pain, area and pain score of hyperalgesia, area and pain score of brush-evoked allodynia and AF. Measurements will be taken prior to (within 15 minutes) and at the 15-, 30-, 60-, 90- and 120-minutes time points post injection. Prior to each injection, 4 intersecting lines forming 45-degree angles will be drawn on the skin using a fine-tipped skin marker for assessment of areas of hyperalgesia and allodynia. The 4 lines will intersect at the injection site and will be marked in 1cm graduations starting from the intersection.

9.2. Measurement of Pain

Pain will be measured on a visual analogue scale (VAS) consisting of a 100 mm line, with 0 representing "no pain'' and 100 "worst pain imaginable." Subjects will be asked to mark the VAS using a single vertical stroke at the point they consider to appropriately reflect their level of pain from the injection of capsaicin (not general pain). A new VAS will be provided for each time-point and subjects will not be allowed to see their previous VAS responses. The VAS will be scored by measuring from the left-hand end of the scale to the point where the subject has marked the line, and the distance in mm recorded.

9.3. Area and Pain Score of Hyperalgesia

The area of mechanical hyperalgesia will be assessed using a standard 24 g von Frey hair. The von Frey hair will be applied at 1-second intervals along each of the 4 lines intersecting at the injection site drawn onto the skin before the injection. Stimulation will begin distal from the injection site and will advance in 1cm increments toward the injection site until a pain response is elicited. Subjects will be asked to report when the von Frey hair first begins to cause any pain sensation or discomfort and the distance of that point from the injection site in centimetres for each line at each time-point will be recorded. The area of hyperalgesia will then be calculated and recorded in the CRF. Pain in response to von Frey stimulation of the hyperalgesic area will be recorded using an 11-point numeric rating scale (NRS) ranging from 0 ("no pain") to 10 ("worst possible pain"). The pain score will reflect the maximum pain experienced during the assessment.

9.4. Area and Pain Score of Allodynia

The area of allodynia will be assessed by sweeping a standard paintbrush at 1-second intervals across each of the 4 lines intersecting at the injection site drawn onto the skin before the injection. Stimulation will begin distal from the injection site and will advance in 1 cm increments toward the injection site until a pain response is elicited. Subjects will be asked to indicate when the brush first begins to cause any pain or discomfort and the distance of that point from the injection site in centimetres for each line at each time-point will be recorded. The area of allodynia will then be calculated and recorded in the CRF. Pain in response to brush stimulation of the allodynic area will be recorded using an 11-point NRS ranging from 0 ("no pain") to 10 ("worst possible pain"). The pain score will reflect the maximum pain experienced during the assessment.

9.5. Area of Flare

The AF will be determined by tracing the outline of visible skin reddening on to a sheet of acetate placed on the skin using a fine-tipped, permanent marker. The area will subsequently be measured using planimetry and the results recorded in the CRF.

10. STATISTICS AND DATA ANALYSIS

10.1. Randomisation and Subject Allocation

Randomisation schemes will be produced by MAC Clinical Research. Separate randomisation schemes will be produced for each of study Part A and study Part B. After informed consent is obtained, subjects will be allocated to a unique screening number.

A simple randomisation scheme will be performed for study Part A, while a blocked randomisation scheme will be used for study Part B. The block size for Part B will be 16, giving 8 blocks in total.

Only subjects who comply with all the inclusion criteria, and none of the exclusion criteria, will be randomised onto the study. The randomisation number will have 5 digital numbers, with the first being the study part (1 for Part A, 2 for Part B), the second being whether a subject is a replacement (0 = original; 1 = replacement), and the last 3 being the subject number; for example, 10011 means the 11th subject originally randomised for Part A, whereas 11011 is the replacement of 10011. All screened subjects should be identifiable throughout the study.

10.2. Sample Size Determination

It is planned to enrol 12 subjects in Part A and 128 subjects in Part B. No formal sample size calculation has been performed. A study of 12 subjects in Part A and 128 subjects in Part B are considered to be sufficient to meet the objectives of the study.

10.3. Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be prepared after finalising the Protocol and before database lock. The specifications in this document will detail the implementation of all the planned statistical analyses in accordance with the principal features stated in the Protocol. The SAP will provide full details of the analyses, data displays, and algorithms to be used for data derivation. Any deviation from the original SAP will be described in the Clinical Study Report.

10.4. Analysis Sets

A subject who withdraws prior to the last planned observation in the study period will be included in the analyses up to the time of discontinuation.

10.4.1. Safety Set

10.4.1.1. Part A

The Safety Set will consist of all subjects who received a dose of the IMP (KLS-GABA or KLS).

10.4.1.2. Part B

The Safety Set will consist of all subjects who received a dose of the IMP (KLS, KLS-GABA, gabapentin, or Placebo).

10.4.2. Pharmacokinetic Set

10.4.2.1. Part A

The PK Set will consist of all subjects who received a dose of the IMP (KLS-GABA or gabapentin) and have evaluable PK data.

10.4.2.2. Part B

The PK Set will consist of all subjects who received a dose of the IMP (KLS, KLS-GABA, gabapentin, or placebo) and have evaluable PK data.

10.4.3. Pharmacodynamic Set

10.4.3.1. Part A

The PD set it not required for Part A of this study.

10.4.3.2. Part B

The PD set will consist of all randomised subjects who received a dose of randomised therapy. Patients will be analysed according to their actual treatment received (a per protocol analysis set). The analyses of efficacy endpoints will use the PD set.

10.5. Statistical Analysis

Separate analyses will be provided for Part A and Part B study.

Appropriate descriptive statistics will be produced, according to the nature of the variable. For continuous data n, mean, standard deviation (SD), median and range (minimum and maximum) will be presented. For categorical data, frequency distributions and percentages will be presented.

All the data collected and derived in the study will be presented in subject data listings.

Statistical analyses will be performed using SAS 9.4.

10.5.1. Subject Disposition and Characteristics

A description of subject disposition will be provided. It will include a summary of the number and percentage of subjects entered into the study, enrolled in the study, and treated as well as number and percentage of subjects completing the study, or discontinuing (overall and by reason for discontinuation). All entered subjects will be accounted for in this summary of disposition. A summary of all protocol deviations will be provided.

Demographic and baseline characteristics, medical history, concomitant medication and treatment compliance will be summarised for all subjects in the Safety Set by treatment.

10.5.2. Safety Statistical Analysis

Safety assessments will include standard laboratory safety evaluations (haematology, biochemistry, coagulation, and urinalysis), vital signs (blood pressure, heart rate and oral temperature), physical examinations, 12-lead ECG and AE monitoring.

10.5.2.1. Adverse Events

All AEs will be listed according to SOC and preferred term (PT) assigned to the event using Medical Dictionary for Regulatory Activities (MedDRA; highest version). Number and percentage of subjects who experienced any AEs will be summarised by treatment. Furthermore, AEs will be summarised by causality and the maximum intensity. Any SAEs and/or AEs that led to withdrawal will be listed.

10.5.2.2. Clinical Laboratory Evaluations

Clinical Laboratory evaluation results will be listed and compared to laboratory reference ranges, with those values outside of the applicable range flagged as high (H) or low (L). The

quantitative laboratory data will be summarised using descriptive statistics for each parameter by treatment and time. Urinalysis data will be listed only. A summary of subjects reporting an abnormal value will be reported.

10.5.2.3. Vital Signs

Vital signs (supine systolic blood pressure, diastolic blood pressure, heart rate and body temperature) will be listed for individual subjects. Summary statistics will be calculated for each parameter by treatment and time.

10.5.2.4. 12-Lead Electrocardiogram

Standard 12-lead ECG parameters (RR, PR, QRS, QTcF intervals and HR) will be listed for individual subjects. Out-of-range ECG values will be flagged as high (H) or low (L). Summary statistics will be calculated for each parameter by treatment and time. Where multiple values are recorded at a timepoint for a subject, the mean of the values will be used in the summary statistics.

10.5.2.5. Physical Examination

Physical examination data will be listed for individual subjects. Summary statistics will be calculated for each parameter by treatment and time.

10.5.3. Pharmacokinetic Statistical Analysis

KLS, KLS-GABA and gabapentin concentrations and parameters will be summarised using all subjects in the PK Set. Full details of the PK analysis will be included in the PK Analysis Plan.

10.5.3.1. Derivation of Pharmacokinetic Parameters (Part A only)

Pharmacokinetic parameters will be derived from plasma concentration data of ketoprofen when given alone (KLS) and ketoprofen and gabapentin when given in combination (KLS-GABA) by noncompartmental analysis. The PK parameters derived to assess the single dose PK of KLS and KLS-GABA are shown in Table 5.

Table 5: Pharmacokinetic Parameters (Part A)

Abbreviation	Definition
C_{max}	Maximum plasma concentration
t_{max}	Time of maximum plasma concentration
AUC_{0-12h}	Area under the plasma concentration-time curve from zero to 12 hours postdose
AUC_{0-24h}	Area under the plasma concentration-time curve from zero to 24 hours postdose
AUC_{0-36h}	Area under the plasma concentration-time curve from zero to 36 hours postdose
AUC_{0-48h}	Area under the plasma concentration-time curve from zero to 48 hours postdose
AUC_{0-t}	Area under the plasma concentration-time curve from zero to the last quantifiable concentration
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from zero to infinity
$t_{1/2}$	Apparent terminal half-life

10.5.3.2. Statistical Analysis of Pharmacokinetic Parameters (Part A only)

The ketoprofen and gabapentin PK parameters AUC_{0-t}, AUC_{0-12h}, AUC_{0-24h}, AUC_{0-36h}, AUC_{0-48h}, $AUC_{0-\infty}$ and $t_{1/2}$ will be generated using noncompartmental methods. C_{max} will be determined directly from the data.

10.5.4. Pharmacodynamic Statistical Analysis

Summaries and descriptive statistics will be produced for each PD parameter. This includes Scores (VAS or NRS) / Area measured (cm^2) for each treatment and timepoint, along with change from baseline in Score / Area.

Mixed Model Repeated Measures (MMRM) will be fit to data for each PD parameter using two groups of models. Group 1 will assess longitudinal changes in Scores / Area against baseline. Group 2 will assess differences in Scores / Area between treatments for each timepoint.

10.5.4.1. Descriptive statistics

Descriptive statistics will be produced for each PD parameter. Separate tables will be produced that report summary statistics for Scores (VAS or NRS) and Area measured (cm^2) for each PD parameter.

Corresponding figures will be produced for each PD parameter, separately for each patient and combined for all patients in a treatment group. Figures that summarise overall mean/median Score/Area across patients will be produced combining all treatment groups.

10.5.4.2. Modelling

Two separate sets models will be fit to the data. Individual models will be fit per treatment group to assess means and change from baseline in score and area for each PD parameter. Combined models will be fit using all treatment groups to assess differences in means and change from baseline in score/area against placebo.

<u>Model Group 1:</u>

The MMRM model will contain a term for timepoint and will contain baseline Score / Area as a covariate and subject as a random effect. An unstructured covariance matrix will be assumed.

If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: toeplitz with heterogeneity, autogressive with heterogeneity, toeplitz, and autoregressive.

Least squares (LS) means will be reported for each visit along with corresponding 95% confidence intervals (CIs).

The model will be fit separately for each treatment group, for the following dependent variables:

A) Score / Area for each PD parameter

B) Change in score / Area for each PD parameter

<u>Model Group 2:</u>

The MMRM model will contain terms for randomised treatment group and timepoint and will contain baseline Score / Area as a covariate and subject as a random effect. An unstructured covariance matrix will be assumed.

If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: toeplitz with heterogeneity, autogressive with heterogeneity, toeplitz, and autoregressive.

Least squares (LS) means will be reported by visit for each randomised treatment group; the difference in LS means between each dose arm and placebo will be presented along with corresponding 95% CIs.

10.5.5. Pharmacokinetic/Pharmacodynamic Statistical Analysis

Further details of the planned PK/PD correlation analysis will be provided in the SAP.

10.6. Handling of Missing or Incomplete Data

Unrecorded values will be treated as missing. Depending on the extent of the missing values, further investigation may be made into sensitivity of the analysis results to the method(s) specified.

11. DATA HANDLING AND RECORD KEEPING

11.1. Collection of Data

Data collected from each completed subject will be recorded on source documents, which will be entered into an eCRF. The Investigator is responsible for ensuring that all sections of the eCRF are completed correctly and that entries can be verified against the source documents. If certain data are not available or not applicable this will be indicated as such within the appropriate area of the eCRF.

Screening failures (subjects who signed consent to take part in the study but were not dosed) will not be entered into the clinical study database.

Data produced by automatic devices with original printouts (i.e., clinical laboratory evaluation results, ECG traces) will be attached to the source documents. Clinical laboratory parameters will be provided in laboratory printouts which are to be signed by the Investigator. Comments on all clinically significant abnormal values will be provided and documented by the Investigator or appropriately recorded within the eCRF.

Adverse Events and Medical History will be reported by the MedDRA SOC and PT; the latest version will be applied to all terms. All Medical History and AEs will be included in the data listings. Furthermore, all Prior Medications and Concomitant Medications will be reported using the WHODRUG categorization; the latest version will be applied to all terms.

All Prior Medications and Concomitant Medications will be summarised within the data listings.

Any missing, implausible, or inconsistent recordings within the eCRFs will be referred to the Investigator using data query validation procedures; will be documented and resolved for each individual subject before database lock is declared.

All processes pertaining to the Data Management activities will be detailed within the Data Management Plan.

11.2. Inspection of Records

Authorised representatives of Dompé will be allowed to conduct site visits to the CRU for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability and subject records, study source documents and any other pertinent records relative to study conduct.

11.3. Retention of Records

The Investigator should maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the IMP for investigation. If it becomes necessary for Dompé or a regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

12. MONITORING, AUDIT AND INSPECTION

12.1. Study Monitoring

Before a CRU can enter a subject into the study, a representative of Dompé/MAC will visit the CRU to:

- Determine the adequacy of the facilities,
- Discuss with the Investigator and other personnel their responsibilities with regard to Protocol adherence, and the responsibilities of Dompé or its representatives. This will be documented in a Clinical Trial Agreement between Dompé and the Investigator.

During the study, a monitor (MAC) will have regular contacts with the CRU, for the following:

- Provide information and support to the Investigator.
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the Protocol, that data are being accurately recorded in the eCRFs, and that IMP accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any Protocol deviations not previously sent to Dompé
- Confirm AEs and SAEs have been appropriately documented within eCRFs and confirm any SAEs have been communicated to Dompé and those SAEs that met criteria for reporting have been provided to the REC.

The monitor will be available between visits if the Investigator or other staff needs information or advice.

The study will be conducted according to MAC SOPs and a copy of the SOPs will be provided to the Sponsor.

12.2. Audits and Inspections

Authorised representatives of Dompé, a regulatory authority, or the REC may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents. The inspection determines whether these activities were conducted, in addition to data being recorded, analysed, and accurately reported according to the Protocol; ICH-GCP and any applicable regulatory requirements. The Investigator is responsible for making contact with Dompé immediately, if approached by a regulatory agency regarding an inspection.

12.3. Quality Control and Quality Assurance

To ensure compliance with GCP and all regulatory requirements, Dompé, may conduct a Quality Assurance Audit.

12.4. Research Ethics Committee (REC)

The Investigator should obtain REC approval for the study. Initial REC approval, and all materials approved by the REC for this study including the subject consent form and recruitment materials, should be maintained by the Investigator and made available for inspection.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Ethical Conduct of the Study

The study will be conducted in accordance with the EU Clinical Trial Directive 2001/20/EC, the ICH guideline for GCP E6(R2) dated December 2016, and the ethical principles laid down in the Declaration of Helsinki. Current regulatory requirements will be followed, as applicable.

13.2. Ethics Review

The final study Protocol, including the final versions of the Informed Consent Forms (ICFs), must be approved or given a favourable opinion in writing by a REC as appropriate. The Investigator should submit written approval to Dompé before enrolling any subject into the study.

The Investigator is responsible for informing the REC of any amendment to the Protocol in accordance with local requirements. In addition, the REC must approve all advertising used to recruit subjects for the study. The Protocol must be reapproved by the REC upon receipt of substantial amendments, as local regulations require.

The Investigator is also responsible for providing the REC with reports of any reportable serious adverse drug reactions from any other study conducted with the IMP. Dompé will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the REC according to local regulations and guidelines.

13.3. Written Informed Consent

Potential subjects will have a detailed verbal presentation of the nature, purpose, risks, and requirements, in addition to receiving detailed written information provided in the Participant Information Sheet. A Patient Information Sheet and ICF will be produced for each part of the study. They will have adequate opportunity to ask the physician presenting the study about any aspect of the study. Subjects will also be notified that they are free to discontinue from the study at any time. The subject will be given the opportunity to ask questions and allowed time to consider the information provided. Once the subject is satisfied that they are willing to participate in the study, they will be asked to sign a copy of the study ICF. The subject's signed and dated informed consent must be obtained before conducting any study procedures. The Investigator must maintain the original, signed ICF. A copy of the signed ICF will be provided to the subject.

Data and samples collected up to the point of withdrawal can only be used after withdrawal if the subject has consented for this. Any intention to utilise such data should be outlined in the consent literature.

A subject may be rescreened for the study once, if:

- They were ineligible at the first screen due to a transient reason, such as an upper respiratory tract infection, which impacted the clinical laboratory results.
- They were eligible at first screen, but unable to take part in the study dates within the Screening window.
- The subject was finally not enrolled in the initial group, e.g., reserve subjects.

In the case of rescreening, only the assessments that were performed more than 28 days before the new dosing date will be repeated. The CRU will maintain a record of all subjects screened (i.e., who signed the ICF) and any subject who is rescreened will be allocated a new screening number. Records up to the time of premature termination should be completed. In the event that a subject does not receive a study treatment, the primary reason will be recorded. A list of the procedures conducted at Screening are presented in the Schedule of Assessments (Appendix 1 and Appendix 2).

Informed consent will be obtained prior to the subject undergoing procedures that are specifically for the purposes of the study.

13.4. End-of-Study

The end-of-study is defined as completion of the clinical activities relating to the follow-up visit by the last subject.

13.5. Notification of Serious Breaches to Good Clinical Practice

A "serious breach" is a breach which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the subjects of the study; or,
- the scientific value of the study.

The Sponsor will be notified immediately of any case where the above definition applies during the study conduct phase. The Sponsor of a clinical study will notify the licensing authority in writing of any serious breach of:

- the conditions and principles of GCP in connection with that study; or
- the Protocol and/or any Protocol amendments relating to the study, within 7 days of an awareness of the breach.

13.6. Confidentiality and Data Protection

By signing this protocol, the Investigator and the Contract Research Organisation (CRO) agree to keep all the information provided by the Sponsor in strict confidentiality and to request the same confidentiality from his/her staff. Study documents provided by the Sponsor (protocols, IB, eCRFs and other materials) will be stored appropriately to ensure confidentiality. The information provided by the Sponsor to the Investigator and to the CRO cannot be disclosed to others without direct written authorisation from the Sponsor, except for the extent necessary to obtain the informed consent from the subjects wishing to participate in the study.

Data on subjects collected in the eCRFs during the study will be documented in a coded way. If, as an exception, for safety or regulatory reasons identification of a subject becomes necessary, the monitor, the Sponsor and the investigator will be bound to keep this information confidential.

The processing of personal data by the Sponsor, the CRO and the Clinical Site shall always be in line with the local regulations, the EU General Data Protection Regulation (GDPR; Regulation EU 679/2016), and the Data Protection, Privacy and Electronic Communications (Amendments etc) (EU Exit) Regulations 2019 (the UK GDPR). Suitable written information will be provided to the study subjects at the time of consenting.

13.7. Publication Policy

The Sponsor agrees that the study results (including negative and inconclusive as well as positive results) can be made publicly available by the Investigator publishing in peer reviewed journals, presenting results at scientific congresses and posting information and results on internet-based public registers and databases.

Study results will be communicated in full to the competent Health Authorities by the submission of a complete clinical study report.

As the Sponsor agrees that the study results can be published by the Investigator, the Investigator agrees to submit any manuscript (abstract, publication, paper, etc.) to the Sponsor before any public disclosure.

This will be done in order to ensure that clinical study results are reported in an objective, accurate and balanced manner. The Sponsor reviews the proposed manuscripts, before submission, within a reasonable period of time (30 to 90 days in relation with the complexity of the work).

The Investigator will also be provided by the Sponsor with the clinical study report and the results of any additional analysis, tables, figures, etc. undertaken for the purposes of the article, in order to take responsibility for the content of the publication(s).

On an exceptional basis, the Sponsor may temporarily delay registration of certain data elements (e.g., compound, name, outcome, measures, etc.) to seek necessary intellectual property protection. This is because early disclosure of such data could, in some circumstances, prevent or negatively impact patentability.

A description of this clinical trial will be available on the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database and on http://www.clinicaltrials.gov.

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15. APPENDICES

15.1. Appendix 1– Schedule of Assessments (Part A)

Schedule of Assessments Part A	**Screening Up to 28 Days**	**Treatment Period 1 and Treatment Period 2 (minimum washout period of 7 days between periods)**		**Post-Study (5 to 7 days post final-dose)**
		Day -1	**Days 1 to 3**	
Informed Consent	X			
Demography	X			
Inclusion/Exclusion Criteria[a]	X			
Medical History	X			
Urine Drugs of Abuse and Breath Alcohol Screen	X	X		
SARS-CoV-2 Test	X	X		
Serology	X			
Study Residency				
Admission		X		
Discharge			Day 3 (48 hours postdose)	
Non-Residential Visit	X			X
KLS-GABA/KLS Administration			Day 1	
Safety Assessments				
Physical Examination	X	X		X
Vital Signs (HR, BP and oral temperature)[b]	X		Predose, 1, 2, 4, 8, 24 and 48 hours postdose	X
12-Lead ECG[c]	X		Predose, 1, 4, 24 and 48 hours postdose	X
Clinical Laboratory Evaluations	X		Predose and 48 hours postdose	X
AE and Concomitant Medication Monitoring	X	X	Predose, 1, 2, 3, 4, 6, 8, 12, 24 and 48 hours postdose	X
Pharmacokinetic Assessments				
Blood Sampling[d]			Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours postdose	

Abbreviations: AE – adverse event; BP – blood pressure; ECG – electrocardiogram; GABA – Gabapentin; HR – heart rate; KLS - Ketoprofen Lysine Salt; SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2.

a A full check of inclusion/exclusion criteria will take place at screening. At all other days to which inclusion/exclusion criteria apply, only those particular inclusion/exclusion criteria will be checked

b Supine only.

c ECG assessments will be conducted within a ±30 minute time window.
d Fourteen samples per subject will be taken per treatment period.

15.2. Appendix 2– Schedule of Assessments (Part B)

Schedule of Assessments Part B	**Screening Up to 28 Days**	**Screening 2 Prior to Day -1**	**Treatment Period**		**Post-Study (5 to 7 days post-final dose)**
			Day -1	**Day 1**	
Informed Consent	X				
Demography	X				
Inclusion/Exclusion Criteria[a]	X				
Medical History	X				
Urine Drugs of Abuse and Breath Alcohol Screen	X		X		
SARS-CoV-2 Test	X		X		
Serology	X				
Study Residency					
Admission			X		
Discharge				12 hours postdose	
Non-Residential Visit	X				X
KLS-GABA/ KLS/Gabapentin/ Placebo Administration				X	
Safety Assessments					
Physical Examination	X				X
Vital Signs (HR, BP and oral temperature)[b]	X		X	Predose, 1, 2, 4, 8 and 12 hours postdose	X
12-Lead ECG[c]	X			Predose, 1, 4 and 12 hours postdose	X
Clinical Laboratory Evaluations	X		X		X
AE and Concomitant Medication Monitoring	X	X	X	Predose, 1, 2, 3, 4, 6, 8 and 12 hours postdose	X
Plasma Concentration Assessments					
Blood Sampling				Predose, pre-capsaicin and 2 hours post capsaicin	

Pharmacodynamic Assessments					
Intradermal Capsaicin Injection		X[d]	X[e]	X[f]	
Pain Measurement		X[g]	X[h]	X[h]	

Abbreviations: AE – adverse event; BP – blood pressure; ECG – electrocardiogram; GABA – Gabapentin; HR – heart rate; KLS - Ketoprofen Lysine Salt SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2.

a A full check of inclusion/exclusion criteria will take place at screening. At all other days to which inclusion/exclusion criteria apply, only those particular inclusion/exclusion criteria will be checked

b Supine only.

c ECG assessments will be conducted within a ±30 minute time window.

d Additional screening visit at least 7 days prior to dosing to determine response to capsaicin and vehicle injections

e At a similar time of day to that anticipated on Day 1

f At estimated T_{max} for KLS alone or KLS-GABA from Part A

g Pain VAS, Flare, Hyperalgesia, Allodynia conducted pre-capsaicin injection and 15 minutes post injection.

h Pain VAS, Flare, Hyperalgesia, Allodynia conducted pre-capsaicin injection and 15, 30, 60, 90 and 120 minutes post injection

15.3. Appendix 3– Sampling Summary

The following table summarises the approximate number of samples and volumes for sampling during the study.

Part A

Sample Type	Sample Purpose	Number of Samples[a] (Volume Per Sample)	Total Volume (mL)
Blood	Haematology	6 (2 mL)	6 mL
Blood	Biochemistry	6 (5 mL)	15 mL
Blood	Pharmacokinetics	28 (8 mL)	224 mL
	Total Blood:		245 mL

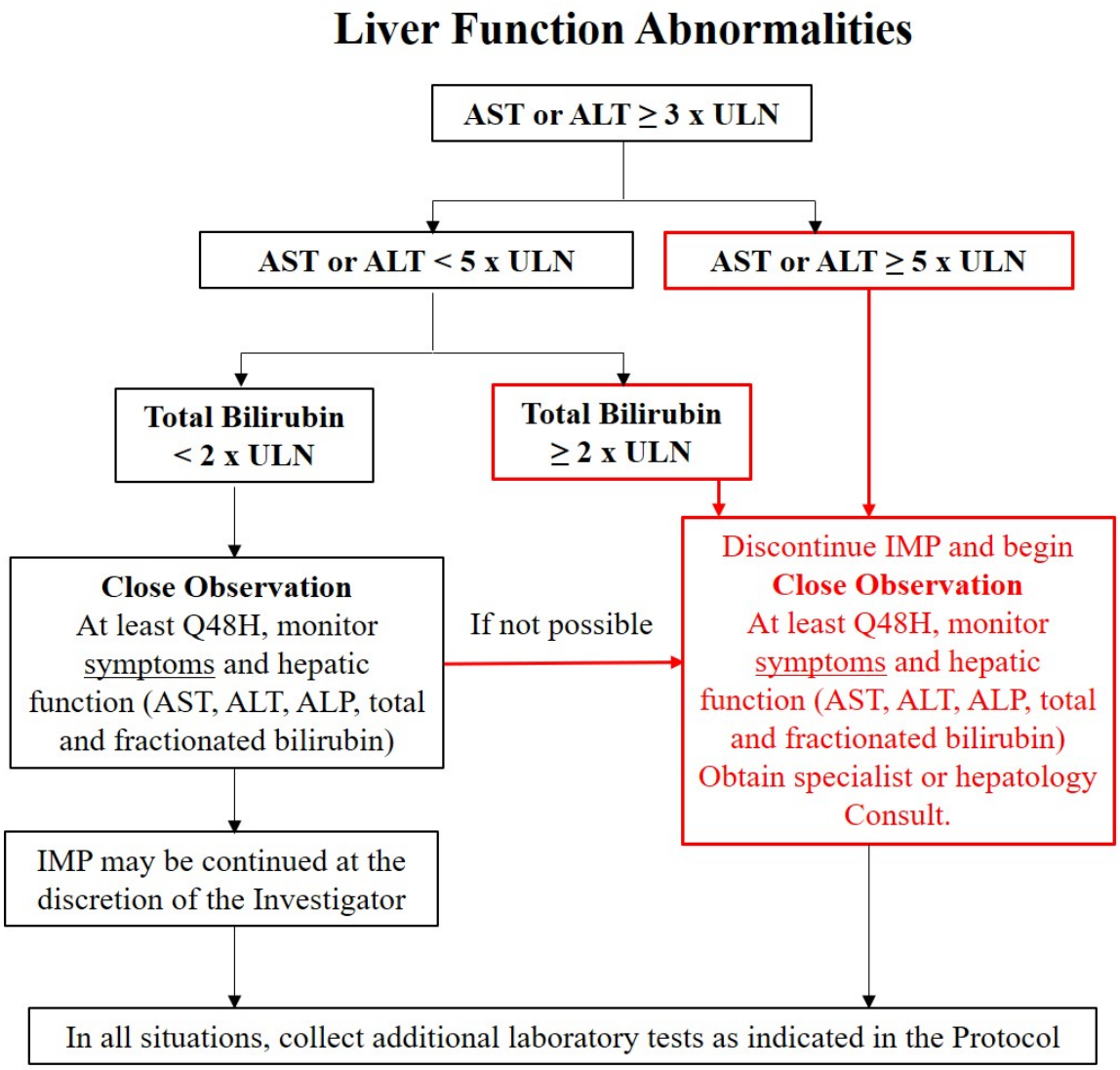
a Additional samples may be drawn if needed for safety reasons. Up to 2 additional pharmacokinetic samples may be taken if needed, in order to define the pharmacokinetic profile.

Part B

Sample Type	Sample Purpose	Number of Samples[a] (Volume Per Sample)	Total Volume (mL)
Blood	Haematology	3 (2 mL)	4 mL
Blood	Biochemistry	3 (5 mL)	10 mL
Blood	Pharmacokinetics	3 (8 mL)	24 mL
	Total Blood:		38 mL

a Additional samples may be drawn if needed for safety reasons. Up to 2 additional pharmacokinetic samples may be taken if needed, in order to define the pharmacokinetic profile.

15.4. Appendix 4



Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; IMP: investigational medicinal product; Q48H: every 48 hours; ULN: upper limit of normal.
* The following tests are required for subjects/patients with AST or ALT ≥3 x ULN and bilirubin ≥2 x ULN: Anti-nuclear antibody, anti-smooth muscle antibody, and type 1 anti-liver kidney microsomal antibodies, in addition to liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver diseases.