	Corporate Medical Department	**Identification Number:** **FORM-000050125**
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		Version Number: **0.7, CURRENT**

CLINICAL STUDY PROTOCOL

A randomized, double-blind, placebo-controlled, parallel arm group study to evaluate the analgesic efficacy and safety of Dexketoprofen trometAmol aNd Tramadol hydrochloride oral fixEd dose combination on moderate to severe acute pain in patients with acute low back pain **DANTE study**	
Sponsor name and address	Menarini International Operations Luxembourg SA. 1, Avenue de la Gare L-1611 Luxembourg. Ph. (+352) 2649761 - Fax (+352) 26497649
Protocol Code	MEIN/18/DEX-LBP/001
EudraCT (or National Clinical Trial Identified Number)	2019-003656-37 NCT05170841
Protocol Phase (if applicable)	IV
Study type and design:	Multicenter, randomized, double-blind, double-dummy, parallel group, placebo-controlled study encompassing 2 study phases: a single-dose phase (first 8 hours) and a multiple-dose phase starting after the single-dose phase.
Protocol Version Number	Version 2 (Amendment 1)
Protocol Version Date	13 September 2021
Coordinating Investigator	Prof. Giustino Varrassi
CRO	IQVIA

Summary of Changes from Previous Version

Document History

Document	Date	Substantial	Region
Amendment 1	13 September 2021	Yes	Global

The overall rationale for this amendment is to update the change in the sample size as per the re-estimation of sample size and to incorporate the changes provided in erratum dated 19 May 2020.

Affected Section(s)	Summary of Revisions Made	Rationale
Section 2. Protocol Synopsis **Section 14.2. Determination of Sample Size**	The statistical power of the study has been revised in order to achieve a desired power level of 80%. The original study power was set at 90%. The sample size for the study has been reduced accordingly from 680 to 510 and the number of patients to be randomized in each treatment arm has been updated (204 patients each in TRAM.HCl and DKP.TRIS/TRAM.HCl treatment groups and 102 patients in Placebo groups). The total number of patients to be screened is changed to 612 patients from 816 patients The text related to the sample size determination and study schema is updated accordingly.	The protocol changes have been implemented to compensate the issues and delays caused by COVID-19 Pandemic situation (patients limited access to hospitals and healthcare workers). We have proposed a sample size re-estimation in order to achieve a desired power level of 80%. The original study power was set at 90%. The estimation of effect size, population variance and α-level were the same used to calculate the original sample size. The power of 80% is deem sufficient to keep the scientific integrity of the study results
Section 2. Protocol Synopsis	In inclusion criterion 6, the reference to exclusion criterion 14 is changed to exclusion criterion 15.	Reference to the correct exclusion criterion has been updated

Section 8.1.1 Inclusion Criteria		To correct the incorrect reference to exclusion criterion
Section 2. Protocol Synopsis **Section 8.1.2 Exclusion Criteria**	Added examples for other analgesics in exclusion criterion 15. For exclusion criterion 16 added selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors in parenthesis for serotonin reuptake inhibitors.	Examples of medication added for clarification Examples of medication added for clarification
Section 10.2 Assessment of Safety **Section 12 Withdrawal Criteria**	Creatinine clearance value defining abnormal renal function is corrected from ≥60 mL/min to ≤60 mL/min.	To correct the error in definition of abnormal renal function. Abnormal renal function for the study is defined as ≤60 mL/min
Section 10.2 Assessment of Safety	Removed the word “locally” with reference to urinalysis.	To remove the reference to local laboratory. All the laboratory evaluations will be performed in central laboratory.
Section 2. Protocol Synopsis **Section 7 Exclusion Criteria**	The number of countries where the study is conducted is reduced to 6 from 8; Italy and Lithuania are removed from the list.	Administrative change

TABLE OF CONTENTS

1. RESPONSIBILITIES

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2. PROTOCOL SYNOPSIS

Title Acronym Sponsor Study Code	A randomized, double-blind, placebo-controlled, parallel arm group study to evaluate the analgesic efficacy and safety of Dexketoprofen trometAmol aNd Tramadol hydrochloride oral fixEd dose combination on moderate to severe acute pain in patients with acute low back pain – DANTE study.
Study product, Dosage and Regimen: -Investigational Product -Reference Therapy (comparator)	Dexketoprofen trometamol (DKP.TRIS) 25 mg/Tramadol hydrochloride (TRAM.HCl) 75 mg film-coated tablet administered orally as a single tablet, every 8 hours. Placebo as one tablet matching DKP.TRIS 25 mg/TRAM.HCl 75 mg. Placebo as two capsules matching TRAM.HCl. Tramadol (TRAM.HCl) 100 mg, as two capsules with 50 mg every 8 hours.
Study Type and Design	This is a multicenter, randomized, double-blind, double-dummy, parallel group, placebo-controlled study encompassing 2 study phases: a single-dose phase (first 8 hours) and a multiple-dose phase starting after the single-dose phase (from t8 h until day 5). 510 eligible patients will be randomized in a 4:4:1:1: ratio to 1 of the 4 possible treatment arms:

Single-dose phase (t0-t8)	**Multiple-dose phase (t8-day5)**
DKP.TRIS/TRAM.HCl n=204	DKP.TRIS/TRAM.HCl
TRAM.HCl n=204	TRAM.HCl
Placebo n=51	DKP.TRIS/TRAM.HCl
Placebo n=51	TRAM.HCl

Phase	IV
Objectives	<u>Primary objective</u>: • To evaluate the analgesic efficacy of DKP.TRIS/TRAM.HCl fixed combination versus placebo in moderate to severe acute low back pain after the first dose (first 8 hours).

	Secondary objectives: • To evaluate the analgesic efficacy of DKP.TRIS/TRAM.HCl fixed combination versus TRAM.HCL 100 mg in moderate to severe acute low back pain after the first dose (first 8 hours). • To evaluate the analgesic efficacy of DKP.TRIS/TRAM.HCl fixed combination in moderate to severe acute low back pain versus TRAM.HCl 100 mg after multiple doses (from t8h until day 5). • To assess the safety and tolerability of DKP.TRIS/TRAM.HCl fixed combination after single and multiple doses.
Endpoints	Primary endpoint: Time to first achieve a numeric rating scale-pain intensity (NRS-PI) score of <4 or a pain intensity reduction ≥30% from drug intake till 8 hours after the first dose (t8h). Secondary endpoints: Single-dose phase: Day 1; t0-t8h • Pain relief (PAR) – verbal rating scale (VRS) scores at each prespecified time point (t15m, t30m, t1h, t1.5h, t2h, t4h, t6h, t8h) over the 8 hours after the first dose. • Total pain relief (TOTPAR) at 4, 6, and 8 hours (TOTPAR4, TOTPAR6, TOTPAR8) after the first dose. • Percentage of maximum TOTPAR (% max TOTPAR) at 4, 6 and 8 hours after the first dose. • Percentage of patients achieving at least 50% of maximum TOTPAR at 4, 6, and 8 hours after the first dose. • Mean Pain Intensity (PI) - visual analogue scale (VAS) scores at each prespecified time points (t15m, t30m, t1h, t1.5h, t2h, t4h, t6h, t8h) over the 8 hours after the first dose. • Summed pain intensity difference (SPID) at 4, 6, and 8 hours (SPID4, SPID6, SPID8) after the first dose.

	• Percentage of maximum SPID (% max SPID) at 4, 6, and 8 hours after the first dose. • Percentage of patients achieving at least 30% of pain intensity reduction versus baseline at 4, 6, and 8 hours after the first dose. • Patient global evaluation (PGE) of the study medication at 8 hours after the first dose. • Time to rescue medication (RM): Time elapsed between treatment administration and the first dose of RM from baseline till 8 hours after the first dose. • Percentage of patients who required RM within the first 4, 6, or 8 hours after the first dose. <u>Multiple-dose phase:</u> from t8h to 8 hour after last dose intake on Day 5 • PAR-VRS scores at each prespecified time point over the multiple-dose phase. • TOTPAR at 24, 48, 72, and 96 hours (TOTPAR24, TOTPAR48, TOTPAR72, TOTPAR96) of the multiple-dose phase. • Percentage of maximum TOTPAR (% max TOTPAR) at 24, 48, 72, and 96 hours of the multiple-dose phase. • Percentage of patients achieving at least 50% of maximum TOTPAR at 24, 48, 72, and 96 hours of the multiple-dose phase. • Pain intensity (PI)- VAS scores at each prespecified time point over the multiple-dose phase. • SPID at 24, 48, 72, and 96 hours (SPID24, SPID48, SPID72, SPID96) of the multiple-dose phase. • Percentage of maximum SPID (% max SPID) at 24, 48, 72, and 96 hours of the multiple-dose phase. • Percentage of patients achieving at least 30% of PI reduction versus baseline at 24, 48, 72, and 96 hours of the multiple-dose phase. • PGE at 96 hours of the multiple-dose phase.

	• Percentage of patients who required RM within 24, 48, 72, and 96 hours of the multiple-dose phase. • Roland Morris Disability Questionnaire (RMQ) at 96 hours of the multiple-dose phase. • Treatment Satisfaction Questionnaire for Medication (TSQM) at 96 hours of the multiple-dose phase. <u>Complete treatment and assessment period</u>: from t0 on Day 1 to 8 hour after last dose intake on Day 5 • Time to first achieve an NRS score <4 or a pain intensity reduction of ≥30% from the first drug intake till 5 days after the first dose, excluding patients assigned to the placebo treatment arms during the single-dose phase. • TOTPAR at 104 hours from the first drug intake till 5 days after the first dose (TOTPAR104), excluding patients assigned to the placebo treatment arms during the single-dose phase. • SPID at 104 hours from the first drug intake till 5 days after the first dose (SPID104), excluding patients assigned to the placebo treatment arms during the single-dose phase. • Time to RM: Time elapsed between the first drug intake till 5 days after the first dose, excluding patients assigned to the placebo treatment arms during the single-dose phase. <u>Exploratory endpoint</u>: Time to first achieve an NRS-PI score <4 AND a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose.
Study Population: Subject's characteristics	Male or female patients aged 18 years to 65 years with acute low back pain of moderate to severe intensity, whose onset of the current acute low back pain episode is within 48 hours prior to Screening. Patients with or without radiculopathy will be included, excluding those with neurological signs, according to the Quebec Task Force classification. Patients experiencing a new episode of low back pain will be eligible only if preceded by a period of

at least 2 months without any low back pain. Patients should be free from analgesic due to previously administered pain killer (immediate or slow release formulations), according to exclusion criteria.
Patients who are judged by the Investigator not to be suitable candidates for the study treatments and the RM based on their medical history, physical examination, concomitant medication (CM) and concurrent systemic diseases will be excluded.

Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Properly executed written informed consent.
2. Male or female patients aged 18 years to 65 years.
3. Patients with acute low back reporting pain of at least moderate intensity at Screening (NRS score ≥ 5). The onset of the current acute low back pain episode is within 48 hours prior to Screening.
4. Patients with or without radiculopathy will be included, excluding those with neurological signs, according to the Quebec Task Force classification.
5. Naïve patients to any low back pain or patients with previous history of low back pain experiencing a new episode, preceded by a period of at least 2 months without any low back pain prior to Screening.
6. Patients free from analgesic (as per exclusion criterion 15) due to previously administered pain killer (immediate or slow release formulations), according to physician's judgment.
7. Females participating in the study must be either:
   - Females of nonchildbearing potential, defined as any woman who had undergone surgical sterilization

(documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or is more than 2 years postmenopausal (defined as no menses for 12 months);

- Females of childbearing potential (following menarche until menopause unless permanently sterile) provided that they have a negative pregnancy test at Screening and are routinely using an effective method of birth control resulting in a low failure rate (ie, combined hormonal contraception, intrauterine device, condoms in combination with a spermicidal cream, male partner sterilization (vasectomy), bilateral tubal occlusion or total sexual abstinence) during the study treatment.

8. Mentally competent and able to understand and give written informed consent prior to Screening.
9. Compliant to undergo all visits and procedures scheduled in the Study.

Exclusion Criteria

1. Patients who are judged by the Investigator not to be suitable candidates for the study treatments and the RM based on their medical history, physical examination, CM and concurrent systemic diseases.
2. Clinically significant abnormalities in the vital signs as per Investigator's judgment.
3. Patients with acute low back pain and radiation to limb with presence of neurologic signs (focal weakness, asymmetry of reflexes, sensory loss in a dermatome, or loss of bowel, bladder, or sexual function) according to Quebec Task Force Classification.
4. History of hypersensitivity to the study treatments, RM or to any other nonsteroidal anti-inflammatory drugs (NSAIDs), or opioids.
5. Known photoallergic or phototoxic reactions during treatment with ketoprofen or fibrates.

	6. History of peptic ulcer, gastrointestinal disorders when taking NSAIDs, gastrointestinal bleeding, or other active bleeding. 7. History of allergy (eg, precipitate attacks of asthma, bronchospasm, acute rhinitis, or cause nasal polyps, urticaria or angioneurotic oedema) to the study treatments, RM or to any other NSAIDs, or opioids. 8. Anamnestic mild to severe renal dysfunction, mild to severe hepatic dysfunction, as per Investigator's judgment. 9. Patients with chronic dyspepsia. 10. Patients with severe heart failure (Class III and Class IV of New York Heart Association [NYHA] Classification). 11. History of hemorrhagic diathesis and other coagulation disorders. 12. History of or current epilepsy or convulsions. 13. Patients with Crohn's disease or ulcerative colitis. 14. Patients receiving monoamine oxidase (MAO) inhibitors (a minimum of 14 days of washout must elapse prior to the Screening). 15. Treatment with topical preparations/medications within 4 hours prior to Screening, anesthetics and muscle r2elaxants within 8 hours prior to Screening, short-acting analgesics (eg, paracetamol) within 4 hours prior to Screening, other analgesics (NSAIDs [eg, ketoprofen ibuprofen, diclophenac]) within 5 half-lives prior to Screening or use of an opioid within the 14 days preceding Screening. 16. Treatment with high doses of salicylates (≥3 g/day), anticoagulants, thrombolytic and antiplatelet agents, heparins, corticosteroids (except inhalers and topical agents), lithium methotrexate, used at high doses of 15 mg/week or more, hydantoins (including phenytoin) and sulphonamides, antiepileptics, antipsychotics, serotonin reuptake inhibitors (selective serotonin reuptake inhibitors [SSRIs] and serotonin norepinephrine reuptake inhibitors [SNRIs]) and tricyclic

Number of Subjects	antidepressants, and analgesics within 48 hours or 5 half-lives (whichever is the longer) prior to Screening. 17. Patients using sedatives (eg, benzodiazepines) and hypnotic agents within 8 hours before Screening. 18. Any chronic or acute painful condition other than the study indication that may interfere with the assessment of the efficacy of the study treatment. 19. Any non-pharmacological interventional therapy for low back pain (physical therapy, acupuncture, massage etc.) one month before Screening. 20. Patients with litigation related to work. 21. Patients with severe dehydration (caused by vomiting, diarrhea, or insufficient fluid intake) within one month prior to Screening. 22. Severe respiratory depression according to physician's judgment. 23. Participation in other clinical studies in the previous 4 weeks. 24. History of drug or alcohol abuse. For the purpose of the study, alcohol abuse is defined as regularly intake of more than 4 units of alcohol per day (1 unit corresponds approximately to 125 mL wine, 200 mL beer, 25 mL spirit). 25. History of any illness or condition that, in the opinion of the Investigator might pose a risk to the patient or confound the efficacy and safety results of the study. 26. Pregnant and breastfeeding women. NOTE: a pregnancy test will be performed on all women of childbearing potential at Screening. 27. Patients presenting any of the contraindications reported for dexketoprofen/tramadol, tramadol or paracetamol (according to the SmPC). 28. Known or suspected serious spinal pathology (eg, metastatic, inflammatory or infective diseases of the spine, cauda equine syndrome, trauma, spinal fracture).

	29. Spinal surgery within the preceding 6 months. Approximately 612 patients will be screened to achieve 510 patients randomly assigned to study treatment given an expected 20% screen failure rate.
Clinical Sites Number of Centers	The study will be conducted in primary care and hospital setting in 6 European countries. Number of centers: 50-60
List of Countries	Croatia, Estonia, Hungary, Latvia, Poland, and Spain.
Study Duration (specify different study phases): First Pts In (FPI) Last Pts Out (LPO)	The individual study participation will last up to 8 days, including: Visit 1 (Day 1): screening phase, randomization and first study treatment administration. Complete treatment and assessment period: from Day 1 to Day 5. After the last dose intake on Day 5, the "follow-up period" will last until Visit 2 (Day 6 +2 days). Visit 2: (Day 6 with an allowed time-window of +2 days): end of study visit. A follow up phone call after Visit 1 and Visit 2 will be performed within 24 hours from results only in case of abnormality and clinically relevant laboratory test according to the investigator judgement.
Study Description	In the single-dose phase patients will receive a single-dose treatment, consisting of 1 film-coated tablet and 2 capsules which have to be orally administered together at the same time (Day 1) and according to Investigator's instructions. The multiple-dose phase will begin 8 hours after the first dose. The patients assigned to DKP.TRIS/TRAM.HCl fixed combination or TRAM.HCL 100 mg during the single-dose phase will continue to receive the same treatment during the multiple-dose phase; however, the patients assigned to receive placebo during the single-dose phase will either receive DKP.TRIS/TRAM.HCl fixed combination or TRAM.HCL 100 mg during the multiple-dose phase.

	The overall clinical phase is planned to start in Q3/2020 and to be completed within Q2/2022.
Statistical Assumptions	Sample size calculation: A sample size of 510 patients is required to detect the difference between DKP.TRIS/TRAM.HCl and placebo and to demonstrate the non-inferiority of DKP.TRIS/TRAM.HCl versus TRAM.HCl for the time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose. A sample size of a total number of 204 patients (102 for each treatment arm) was considered appropriate for detecting the superiority of DKP.TRIS/TRAM.HCl versus Placebo, assuming a power of 80%, alpha of 0.05, and a hazard ratio of 1.5 with a relative Wald confidence interval of 1.17 to 1.97 and the probability of event of 0.961 and 0.835 in the treatment and placebo groups, respectively (based on previous studies).. Additionally, a total number of 408 patients (204 for each treatment arm) is sufficient for assessing the non-inferiority of DKP.TRIS/TRAM.HCl versus TRAM.HCl, assuming a hazard ratio of 1.06, a non-inferiority margin of 0.8, a power of 80%, alpha of 0.025, and proportions of events of 96.1% and 94.7%, respectively (based on previous studies). The 510 patients will be randomized in a 4:4:1:1 ratio (204 for DKP.TRIS/TRAM.HCl, 204 for TRAM.HCl and 102 for placebo - 51 switching to DKP.TRIS/TRAM.HCl and 51 switching to TRAM.HCl in the multiple dose phase). Assuming an approximately 20% screen failure rate, 612 patients are expected to be screened.

	Analysis populations: The following populations will be considered for the statistical analysis: • Safety population: All patients randomized who have received at least 1 dose of the study treatment. • Intention-to-treat (ITT) population: All patients randomized. • Per-protocol (PP) population: All patients of the ITT population who have not experienced major protocol violations. Efficacy analyses will be performed using the ITT population or PP population as defined in the SAP. The PP population will be used to perform confirmatory analyses and to assess non-inferiority. Primary efficacy analysis: The primary efficacy variable, time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose, will be analyzed for the superiority of DKP.TRIS/TRAM.HCl versus placebo on the ITT population using a Cox Proportional Hazard (CPH) model with treatment, baseline PI categories, and baseline radiculopathy categories as covariates. A two-sided significance level of 5% will be used. In the case where the proportional hazard assumption is not satisfied, additional analyses that permit relaxation of the assumption will be implemented. Secondary efficacy analyses: The primary efficacy variable, time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose, and all the secondary endpoints will be used to assess the

	non-inferiority of DKP.TRIS/TRAM.HCl versus TRAM.HCl with one-sided significance level of 2.5%. Non-inferiority hypothesis will be satisfied if the lower limit of the confidence interval is greater than a pre-specified non-inferiority margin. In the case where non-inferiority is confirmed on the PP set, the superiority of DKP.TRIS/TRAM.HCl versus TRAM.HCl will be also tested on the ITT. All the secondary endpoints related to the single phase will be also analyzed for the superiority of DKP.TRIS/TRAM.HCl versus placebo. Non-inferiority will be tested on the PP population and in addition for the secondary endpoints of primary interest (TOPAR24, TOTPAR48) also on the ITT populations. Superiority will only be tested on the ITT population, providing that non-inferiority is confirmed on the PP population. All the secondary endpoints will be tested through an ad hoc inferential analysis, as reported below: • Time to first achieve an NRS-PI score <4 and/or a pain intensity reduction of ≥30% will be analyzed analogously to the primary efficacy variable. • Secondary efficacy variables with quantitative outcome: o NRS-PI, SPIDs, %max SPIDs, TOTPARs, %max TOTPARs, and TSQM will be analyzed by an analysis of covariance (ANCOVA) with treatment and the baseline PI-NRS as covariates. o Roland Morris Disability Questionnaire will be analyzed using ANCOVA with treatment and the baseline RMQ score as covariates. o PGE and PAR-VRS (ordinal variables) will be analyzed by Wilcoxon rank-sum test.

	• Secondary efficacy variables with binary outcomes will be tested using a Chi-squared test. • Time to first use of RM will be assessed using a Log-rank test. • The amount of RM consumption and the number of patients using RM will be descriptively analyzed. Missing values will be handled using different strategies: • Single imputation methods: single missing values between measurements will be linearly interpolated; if more consecutive data are missed, a last observation carried forward (LOCF) method will be applied. • Multiple imputation approach: if a Missing At Random (MAR) pattern of missing data is detected, missing values will be replaced by using a multiple imputation approach. • No imputation: missing values will not be replaced. In order to minimize and evaluate the impact of RM on efficacy assessment, values collected after the RM intake will be imputed by using different strategies: • Single imputation methods: during the single-dose phase, PI will return to its baseline level and PAR to zero (Baseline Observation Carried Forward [BOCF]). During the multiple-dose phase, PI and PAR recorded during the 6 hours after the intake of RM will be replaced with the LOCF or worst observation carried forward (WOCF) in case the assessment immediately before intake is missed. • Estimated approach:

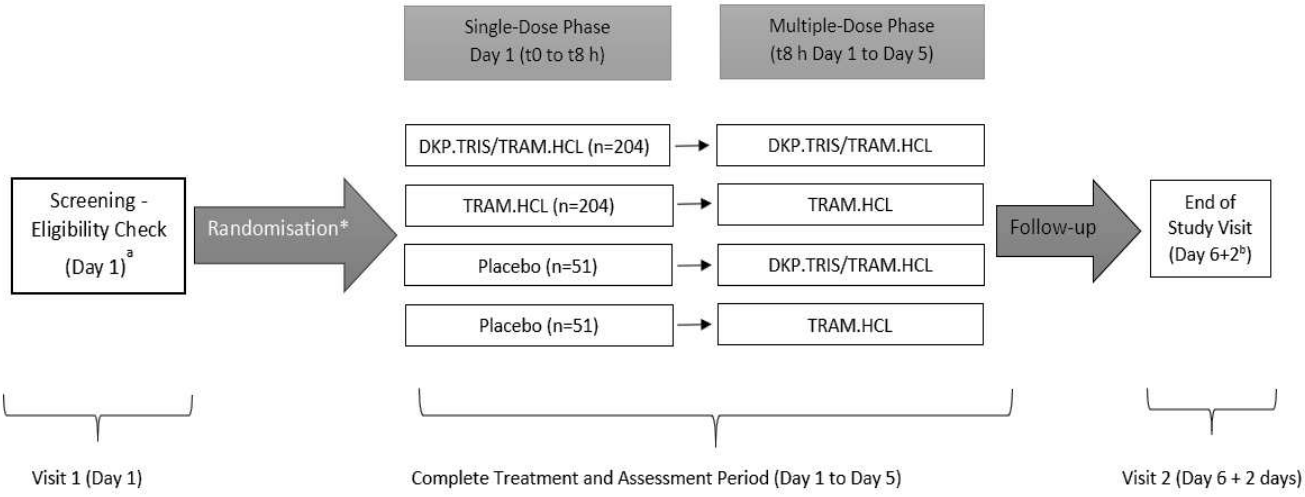
	○ Treatment Policy Strategy: values collected are used regardless of whether or not the RM is taken without any imputation. ○ Hypothetical Strategy: a scenario is envisaged in which the intake of RM would not occur. Values collected for the 6 hours after the RM intake will be considered as missed, and they will be imputed by using a multiple imputation approach. <u>Safety analyses</u>: • Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The incidence of each treatment emergent adverse events (TEAEs) will be summarized by system organ class (SOC), preferred term (PT) and treatment. • Reasons for early treatment termination will be summarized by treatment. • Laboratory findings will be summarized as shift tables by treatment. • Clinically significant abnormal findings in vital signs and physical examination will be listed by treatment. • Safety analyses will be run on the safety population.

3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	DEFINITION
ADR	Adverse drug reaction
AE	Adverse event
ANCOVA	Analysis of covariance
AUC	Area under the curve
BOCF	Baseline observation carried forward
CM	Concomitant medication
DKP.TRIS	Dexketoprofen trometamol
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report forms
GCP	Good Clinical Practice
HA	Health Authority
ICF	Informed consent form
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
ITT	Intention-to-treat
LBP	Low back pain
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical Rating Scale
NSAID	Nonsteroidal anti-inflammatory drugs
PAR	Pain relief
PGE	Patient Global Evaluation
PI	Pain intensity
PP	Per-protocol
RM	Rescue medication
RMQ	Roland Morris Disability Questionnaire

SAE	Serious adverse event
SAP	Statistical analysis plan
SOP	Standard operating procedures
SPID	Summed Pain Intensity Difference
TEAE	Treatment emergent adverse event
TOTPAR	Total pain relief
TRAM.HCl	Tramadol hydrochloride
TSQM	Treatment Satisfaction Questionnaire for Medication
VAS	Visual Analogue Scale
VRS	Verbal rating scale

4. STUDY SCHEME



*Subject will be randomized in a 4:4:1:1 ratio to 1 of the 4 possible treatment arms.

[a] A follow up phone call after Visit 1 will be scheduled only in case of abnormality and clinically relevant laboratory test according to the investigator is observed in laboratory test results performed at Screening.

[b] A follow up phone call after Visit 2 will be scheduled only in case of abnormality and clinically relevant laboratory test according to the investigator is observed in laboratory test results performed at the end of study visit (Visit 2).

4.1 Study Flow Chart

PROCEDURE	VISIT 1 Eligibility Check[a]	COMPLETE TREATMENT AND ASSESSMENT PERIOD					VISIT 2 END OF STUDY[c]
		Single-Dose Phase Day 1			Multiple-Dose Phase Day 1 to Day 5[b]		
	Screening (Day 1)	t0	t15m, t30m, t1h, t1.5h, t2h, t4h, t6h	t8h	From 2nd Dose to Last Dose on Day 5	8h After Last Study Dose	Day 6 +2 Days (Allowed Window)
Informed consent	X						
Demographics	X						
Inclusion/Exclusion criteria	X						
Medical history	X						
Physical examination	X						X
Height and weight	X						
Vital signs (HR, BP)	X						X
Safety laboratory tests	X						X
Pregnancy test	X						X
e-Diary instructions, dispensing and training	X						
Return of e-Diary, IMP, RM and empty blister							X
IMP and RM dispensation	X						
Randomization to treatment	X						
NRS- PI	X	X	X	X	X *(every day BEFORE and 2h AFTER every dose intake)*	X	
PAR-VRS			X	X	X *(every day BEFORE and 2h AFTER every dose intake)*	X	
PGE				X		X	
Roland Morris Disability Questionnaire		X				X	

PROCEDURE	**VISIT 1** Eligibility Check[a]	**COMPLETE TREATMENT AND ASSESSMENT PERIOD**					**VISIT 2 END OF STUDY[c]**
		Single-Dose Phase Day 1			Multiple-Dose Phase Day 1 to Day 5[b]		
	Screening (Day 1)	t0	t15m, t30m, t1h, t1.5h, t2h, t4h, t6h	t8h	From 2nd Dose to Last Dose on Day 5	8h After Last Study Dose	Day 6 +2 Days (Allowed Window)
Treatment Satisfaction Questionnaire						X	
IMP and RM return and accountability							X
Concomitant/prohibited medication	Throughout the study period						
Adverse Events	Throughout the study period						

[a] A follow up phone call after Visit 1 will be performed within 24 hours from results only in case of abnormality and clinically relevant laboratory test according to the investigator judgement.

[b] After the last dose intake on Day 5, the “follow-up period” will last until Visit 2.

[c] A follow up phone call after Visit 2 will be performed within 24 hours from results only in case of abnormality and clinically relevant laboratory test according to the investigator judgement.

5. STUDY RATIONALE AND BACKGROUND INFORMATION

5.1 Low Back Pain

According to the National Institute for Health and Care Excellence (NICE) guidelines, low back pain (LBP) is defined as tension, soreness, and/or stiffness in the lower back region (bottom of rib cage to buttock creases) for which no specific cause can be identified[1]. Low back pain is the leading contributor to years lived with disability. The estimated point prevalence of nonspecific LBP is 18%. Low back pain imposes an enormous economic burden on healthcare systems and affects individuals' daily lives. Hence, there is a need for effective strategies to minimize the impact of LBP.

A search including 15 clinical practice guidelines for the management of LBP in primary care were performed for the period from 2008 to 2017 in electronic databases. For acute LBP, most guidelines endorsed recommendations for patient education, reassurance about the favourable prognosis and advice on returning to normal activities, avoiding bed rest, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and weak opioids for short periods where necessary.[2]

In the literature, several NSAIDs and opioids (diclofenac[3], piroxicam[4], paracetamol[5], oxycodone/acetaminophen, naproxen with cyclobenzaprine[6], tramadol/paracetamol[7]) were evaluated for their efficacy in an acute LBP model in comparison with placebo with conflicting results.

In spite of the great variety of analgesics available, the management of patients suffering from pain still continues to be inadequate. Due to the subjective component of pain, the problems associated with making a diagnosis or the fear of the adverse drug reactions (ADRs) associated with some drugs, patients are frequently undertreated for acute and chronic situations.[8,9,10,11] Clinical experience has shown that in patients with moderate to severe pain, it is difficult to obtain effective analgesia with a single drug (monotherapy); and therefore, analgesic drugs are commonly combined (multimodal analgesia) in order to obtain optimal control of pain.

5.2 Investigational Medicinal Product: Dexketoprofen Benefits

Menarini Ricerche has developed a fixed combination of dexketoprofen trometamol (DKP.TRIS) and tramadol hydrochloride (TRAM.HCl), two analgesics with different mechanisms of action, for the

treatment of moderate to severe acute pain, based on the rationale that multimodal analgesia is necessary in most patients suffering from acute and chronic pain, particularly of moderate to severe intensity. DKP.TRIS and TRAM.HCl are well-known and widely used analgesics and have been available in European countries for a very long time.

The rationale for combining DKP.TRIS and TRAM.HCl relies on the following:

- The drugs have a different mechanism of action. The former exerts its antinociceptive activity mainly at the peripheral level, whereas the latter is a centrally acting analgesic.
- The drugs have a different and complementary pharmacokinetic profile:
  - DKP.TRIS is characterized by a fast absorption and a quick onset of action
  - TRAM.HCl maintains a long analgesic effect (especially over multiple dose).

Consequently, the combination of these substances is expected to result in an improved effectiveness above the level achieved by each single substance. This pharmacodynamic and pharmacokinetic rationale is supported by nonclinical and clinical evidence. Data on the single components are reported below.

Dexketoprofen trometamol

Dexketoprofen trometamol is the tromethamine salt of the S-(+) enantiomer of ketoprofen, an analgesic, anti-inflammatory and antipyretic drug, which belongs to the NSAIDs group (M01AE). The mechanism of action of NSAIDs is related to the reduction of prostaglandin synthesis by the inhibition of cyclooxygenase (COX) pathway. DKP.TRIS has been demonstrated to be an inhibitor for COX-1 and COX-2 activities in experimental animals and humans. It has been shown in different studies that the enantiomer S-(+) of ketoprofen suppresses the synthesis of prostaglandins, whereas the enantiomer R-(-) is inactive or almost inactive.[12,13]

Clinical studies performed on several pain models demonstrated effective analgesic activity of DKP.TRIS. The onset of its analgesic activity was shown to be approximately at 30 minutes after administration, with analgesic effect persisting for 4 to 6 hours.[14,15,16,17,18,19]

After oral administration of DKP.TRIS to humans, the maximum plasma concentration (C_{max}) is reached at 30 minutes (range 15 to 60 minutes). The elimination half-life value of DKP.TRIS is 1.65 hours. The main elimination route for DKP.TRIS is glucuronide conjugation followed by renal excretion. After administration of DKP.TRIS, only the S-(+) enantiomer is obtained in urine, demonstrating that no conversion to the R-(-) enantiomer occurs in humans. When administered concomitantly with food, the area under the curve (AUC) does not change, however the C_{max} of DKP.TRIS decreases, and its absorption rate is delayed (increased time to maximum plasma concentration [t_{max}]).[20]

In multiple-dose pharmacokinetic studies, it was observed that the AUC after the last administration is not different from that obtained following a single dose, indicating that no drug accumulation occurs.[21]

Oral DKP.TRIS (as 12.5 mg and 25 mg film-coated tablets) is currently approved in all European countries and in several non-European countries (for a total of 62 countries world-wide), with a large cumulative experience of use. It is indicated for the symptomatic treatment of pain of mild to moderate intensity, such as musculo-skeletal pain, dysmenorrhoea and dental pain. According to the nature and severity of pain, the recommended dosage is generally 12.5 mg every 4 to 6 hours or 25 mg every 8 hours. The total daily dose should not exceed 75 mg.[22]

DKP.TRIS is also available on the market as a 50 mg/2 mL injectable formulation to be administered either by intramuscular or by intravenous route, which is indicated for the symptomatic treatment of acute pain of moderate to severe intensity, such as post-operative pain, renal colic and LBP. The recommended dose is 50 mg every 8 to 12 hours. If necessary, the administration can be repeated 6 hours apart. The total daily dose should not exceed 150 mg.[23]

Tramadol hydrochloride

TRAM.HCl is a centrally acting analgesic (NO2A X 02). (+)-Tramadol and its main metabolite (+)-O-demethyltramadol [(+)-M1] are non-selective pure agonist at mu (μ), delta (δ) and kappa (κ) opioid receptors with a higher affinity for the μ receptor. Other mechanisms which contribute to its analgesic

effect are inhibition of neuronal re-uptake of noradrenaline [(-)-tramadol] and enhancement of serotonin release [(+)-tramadol]. In contrast to morphine, analgesic doses of TRAM.HCl over a wide range have no respiratory depressant effect; gastrointestinal motility is also less affected, and effects on the cardiovascular system tend to be slight. The potency of TRAM.HCl is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine. The mean absolute bioavailability is approximately 70%, irrespective of the concomitant intake of food. Following a single oral dose administration of TRAM.HCl 100 mg to young healthy volunteers, plasma concentrations are detectable within approximately 15 to 45 minutes with a mean t_{max} of 1.6 to 2 hours. Elimination half-life ($t_{1/2,ß}$) is approximately 6 hours. In humans TRAM.HCl is mainly metabolised by means of N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Among 11 metabolites found in the urine, only M1 is pharmacologically active and animal experiments have shown that it is more potent than the parent substance by the factor 2 - 4. Its half-life ($t_{1/2,ß}$) is 7.9 hours (range 5.4 - 9.6 hours), approximating that of TRAM.HCl. The inhibition of one or both types of the isoenzymes cytochrome P450 3A4 (CYP3A4) and cytochrome P450 2D6 (CYP2D6) involved in the biotransformation of TRAM.HCl may affect the plasma concentration of TRAM.HCl or its active metabolite. TRAM.HCl and its metabolites are almost completely excreted via the kidneys. TRAM.HCl has a linear pharmacokinetic profile within the therapeutic dosage range.[24,25]

Oral TRAM.HCl is currently authorised over 90 countries as 50 mg to 400 mg different formulations (capsules, tablets and extended-release formulations). It is indicated for the treatment of moderate to severe pain. The starting dose in case of acute pain is 100 mg, and the recommended unitary dose is between 50 mg and 100 mg not taken more frequently than every 4 hours, with a maximum of 400 mg/day.[25]

5.2.1. Pre-clinical data on the co-administration of dexketoprofen trometamol and tramadol Hydrochloride

The relevant nonclinical evidence of the fixed combination of DKP.TRIS and TRAM.HCl for the treatment of acute pain of moderate to severe intensity has been established for the two separate products as well as in pharmacological and toxicological studies of the combination of DKP.TRIS and TRAM.HCl performed by Menarini or reported in the literature. In order to further support the rationale and to provide data on the safety use of the combination of DKP.TRIS and tramadol,

pharmacodynamic, safety pharmacology, toxicokinetic, and toxicological studies have been carried out. The co-administration of DKP.TRIS with TRAM.HCl demonstrated a statistically significant improvement of analgesia and a more prolonged effect compared with the single drug administration.

Safety pharmacology studies indicate that DKP.TRIS alone and in association with TRAM.HCl has no significant effect on hERG current and on the electrocardiogram (ECG) in conscious dogs and consequently do not possess any liability for QT prolongation. The effects of dexketoprofen, TRAM.HCl and their combination on gastrointestinal transit (GIT) were investigated in male mice. The results showed that DKP.TRIS antagonized in a dose-dependent fashion the inhibition of the GIT induced by TRAM.HCl. Also, the repeated (13-weeks) oral concomitant administration of DKP.TRIS and TRAM.HCl does not indicate new significant toxicological effects in the rat. Toxicokinetic evaluation shows that the pharmacokinetic parameters of dexketoprofen, tramadol and M1 (O-desmethyltramadol) are similar following their administration as single agents or when combined.

5.2.2. Clinical development of dexketoprofen trometamol and tramadol hydrochloride fixed combination

The clinical development of the DKP.TRIS/TRAM.HCl fixed combination started with a Phase I safety and pharmacokinetics study (DEX-TRA-PK) that indicated that there were no drug-drug interactions between DKP.TRIS and TRAM.HCl and that the concomitant administration, as a single oral dose in healthy subjects, was well tolerated.

A Phase II dose-finding study (DEX-TRA-02) performed in the most frequently used model of acute nociceptive pain of moderate to severe intensity (impacted third mandibular molar tooth extraction), indicated that DKP.TRIS (12.5 mg and 25 mg) and TRAM.HCl (37.5 mg and 75 mg) given as 4 different combinations and as single component were all effective in the treatment of moderate to severe acute pain at 4 and 6 hours post dosing, thus confirming the value of combining the fast active DKP.TRIS with the long-lasting TRAM.HCl efficacy. The study results also allowed for the selection of DKP.TRIS/TRAM.HCl 25 mg/75 mg as the optimum combination of doses to be further evaluated in the subsequent Phase III pivotal studies.

The Phase III studies (DEX-TRA-04 and DEX-TRA-05) results provided robust evidence of the superiority of DKP.TRIS/TRAM.HCl 25 mg/75 mg over the single components, dexketoprofen 25 mg

and tramadol at higher dose (100 mg) (following single and repeated-dose administration), in two recognised models of visceral and somatic moderate to severe acute pain, namely abdominal hysterectomy and hip arthroplasty, respectively. The good safety profile observed was fully in line with that previously established for these agents in monotherapy.

The Phase IIIB study (DEX-TRA-06) results provided robust evidence of the superiority of DKP.TRIS/TRAM.HCl 25 mg/75 mg over PARACETAMOL/TRAM.HCL 650 mg/75 mg (a fixed dose combination already available in the market) in the well-known model of acute nociceptive pain of moderate to severe intensity (impacted third mandibular molar tooth extraction). In this single-dose study, the good safety profile observed was fully in line with that previously established.

Phase I study (DEX-TRA-PK)

The DEX-TRA-PK was an open, randomised, three-sequence, three-session, cross-over, Phase I study, conducted in one single investigational site in Italy. A total of 30 Caucasian healthy subjects (17 men and 13 women, aged 18 to 54 years, who had previously tolerated a test dose of DKP. TRIS 12.5 mg + TRAM.HCl 50 mg), divided in 3 cohorts of 10 subjects, were assigned to receive, according to a cross-over design, one single oral dose of DKP.TRIS 25 mg, TRAM.HCl 100 mg and of both drugs given as extemporaneous combination, in 3 different study sessions separated by a minimum 7-day wash-out period. On each study session, serial blood samples were withdrawn from the subjects for pharmacokinetic assessment. Standard safety parameters were measured during each of the 3 study sessions, with a final safety follow-up visit performed 7 to 10 days after the last treatment intake. The study results showed that DKP.TRIS and TRAM.HCl pharmacokinetic parameters were similar when comparing both drugs administered as single agents and in combination. The rate and the extent of availability (C_{max} and AUC) of DKP.TRIS, (+)-tramadol, (–)-tramadol and (+)-M1 was unaffected by the co-administration. Therefore, it was concluded that there was no drug-drug interaction between TRAM.HCl 100 mg and DKP.TRIS 25 mg when concomitantly orally administered to healthy subjects. Moreover, the concomitant administration was well tolerated without raising any safety concerns.

Phase II study (DEX-TRA-02)

The DEX-TRA-02 was a multicentre, randomised, double-blind, double-dummy, parallel, placebo and active-controlled, single-dose Phase II, dose-finding study aimed at evaluating the analgesic efficacy and safety of DKP.TRIS (12.5 mg and 25 mg) and TRAM.HCl (37.5 mg and 75 mg) given as 4 different combinations and as single components, in comparison to placebo, on moderate to severe acute pain following impacted third mandibular molar tooth extraction. An active control (ibuprofen 400 mg) was included in order to validate the pain model, in compliance with the regulatory guidelines on clinical investigation of medicinal products for treatment of nociceptive pain (CPMP/EWP/612/00).

The design included a total of 10 balanced treatment arms, with the 4 combinations of DKP.TRIS/TRAM.HCl (12.5 mg/37.5 mg, 12.5 mg/75 mg, 25 mg/37.5 mg and 25 mg/75 mg), the 4 corresponding single treatments, placebo and ibuprofen 400 mg. A total of 611 patients (247 males and 364 females, aged 18 to 64 years) experiencing moderate to severe pain (Visual Analogue Scale, [VAS] ≥ 40mm and Verbal Rating Scale, [VRS] ≥ 2) after the extraction of at least one impacted third mandibular molar tooth were randomised and received one single oral dose of the assigned study treatment. Rescue medication consisting of paracetamol (1 g, every 6 to 8 hours) was available on request during the 24-hour post-dose period.

The analgesic efficacy evaluation was based on the patients' electronic diary (e-Diary) scores of pain intensity (PI) and pain relief (PAR) measured on VRS at regular intervals over a 24-hour postdosing period, the patient global evaluation (PGE) at the end of the assessment period and the use of rescue medication (RM). After use of RM, PI returned to its baseline level and PAR to zero for all subsequent time points (baseline observation carried forward [BOCF]).

Safety was assessed by evaluation of any change in the physical examination, vital signs, 12- lead ECG, and laboratory safety tests post-dose versus baseline. Recording and monitoring of adverse events (AEs) were conducted during the entire study period. The efficacy analysis was run on the Intention-to-treat (ITT) population, which included 606 patients (with balanced allocation into the 10 treatment arms). The percentage of responders (achievement of at least 50% maximum total pain relief [max TOTPAR]) over the 6-hour post-dosing period (primary endpoint; Figure 1) was significantly

superior to placebo for all DKP.TRIS/TRAM.HCl combinations ($p < 0.0001$ for each comparison, except $p = 0.0009$ for DKP12.5/TRAM37.5); with the highest percentage of responders achieved in the DKP.TRIS/TRAM.HCl 25 mg/75 mg group (72% versus 10% in the placebo group). The percentage of responders was also statistically superior to placebo for all combinations over 4 hours and it remained statistically superior (except for DKP.TRIS/TRAM.HCl 12.5 mg/37.5 mg) over 8 and 12 hours.

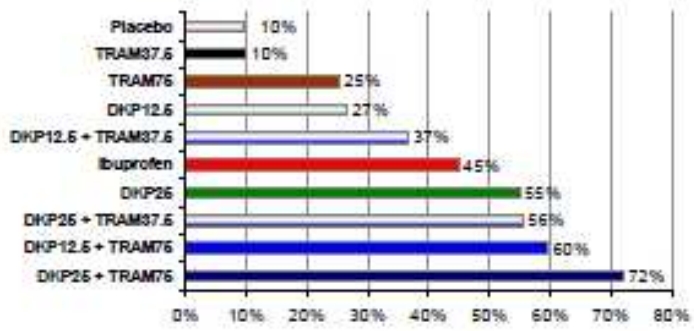


Figure 1: Primary Endpoint - Percentage of responders (achievement of at least 50% max TOTPAR) over 6 hours; max TOTPAR corresponded to the theoretical maximum weighted sum of the PAR scores, according to a 5-point VRS (0 = 'none' to 4 = 'complete'); ($p < 0.0001$ for each comparison; except $p = 0.0009$ for DKP.TRIS/ TRAM.HCl 12.5mg/37.5mg).

The analysis of sum of pain intensity differences (SPID), TOTPAR and derived variables (% max SPID and % max TOTPAR) over 4, 6, 8, and 12 hours showed that all combinations were significantly superior to placebo, with the best results achieved with DKP.TRIS/TRAM.HCl 25 mg/75 mg. The time to RM was significantly longer for all combinations than for placebo, with DKP.TRIS/TRAM.HCl 12.5 mg/75 mg and DKP.TRIS/TRAM.HCl 25 mg/75 mg presenting the longest time to RM (median time [95% confidence interval,CI]): 8.5 (5.9 to 13.0) hours and 8.1 (6.3 to 13.4) hours respectively, versus 1.4 (1.2 to 1.8) hours in the placebo group. The percentage of patients using RM over 6 hours was significantly inferior in the groups DKP.TRIS/TRAM.HCl 12.5 mg/75 mg, DKP.TRIS/TRAM.HCl 25 mg/37.5 mg and DKP.TRIS/TRAM.HCl 25 mg/75 mg than in the placebo group (46.8%, 39.7% and 37.7% respectively versus 72.6%), with the DKP.TRIS/TRAM.HCl 25 mg/75 mg group presenting the lowest percentage. The difference was still significant for DKP.TRIS/TRAM.HCl 25 mg/75 mg over

8 hours (47.5% versus 72.6%). The analysis of PGE showed the superiority of all combinations versus placebo, with the higher scores also in the DKP.TRIS/TRAM.HCl 25 mg/75 mg group.

The study results indicated that all combinations were effective in the treatment of moderate to severe acute pain at 4 and 6 hours post-dose, with DKP.TRIS/TRAM.HCl 25 mg/75 mg, DKP.TRIS/TRAM.HCl 12.5 mg/75 mg and DKP.TRIS/TRAM.HCl 25 mg/37.5 mg remaining also effective over 8 and 12 hours, thus confirming the value of combining the fast active DKP.TRIS with the long lasting TRAM.HCl efficacy. DKP.TRIS/TRAM.HCl 25 mg/75 mg presented consistent superior efficacy in all parameters of analgesia tested. All combinations were well tolerated, presenting a safety and tolerability profile fully in line with that previously known for DKP.TRIS and TRAM.HCl as single agents.

The DEX-TRA-02 study results also allowed for the selection of DKP.TRIS/TRAM.HCl 25 mg/75 mg as the optimum combination of doses to be further investigated in the subsequent Phase III pivotal studies. Based on the analysis of the percentage of responders over 4, 6, 8, and 12 hours and conversely the median time to RM (and also taking into account the recommended doses for the single agents, based on their pharmacokinetic profiles), the necessity of re-dosing with DKP.TRIS/TRAM.HCl 25 mg/75 mg in order to maintain an adequate analgesic effect was expected to be every 8 hours. Therefore, the posology/regimen selected for progressing into the confirmatory Phase III trial was DKP.TRIS/TRAM.HCl 25 mg/75 mg to be administered every 8 hours.

Phase III confirmatory studies

DEX-TRA-04 and DEX-TRA-05 were two multicentre, randomised, double-blind, double-dummy, parallel, placebo- and active-controlled, Phase III, registration studies, aimed at evaluating the superior analgesic efficacy and safety of the selected dexketoprofen/tramadol 25 mg/75 mg oral fixed-combination in comparison with the single components (dexketoprofen 25 mg and tramadol 100 mg) following single and repeated-dose administration, on moderate to severe acute pain after abdominal hysterectomy (DEX-TRA-04) and total hip arthroplasty (DEX-TRA-05), two recognised models of visceral and somatic moderate to severe acute pain (CPMP/EWP/612/00), frequently used in the clinical evaluation of analgesic drugs.

Both studies were conducted in parallel and according to similar design and objectives. On the day after surgery, after cessation of the post-operative analgesia, a total of 606 patients (DEX-TRA-04) and 641 patients (DEX-TRA-05) experiencing pain of moderate to severe intensity (VAS ≥40) were randomised and received the first dose of the assigned study treatment. The treatment period consisted of a single-dose phase (first eight hours after the first dose) followed by a multiple-dose phase (subsequent six doses, in case of DEX-TRA-04 or subsequent 12 doses, in case of DEXTRA-05). Each dose of study medication was separated by an eight-hour interval. During the single-dose phase, patients received one of four possible treatments (dexketoprofen/tramadol 25 mg/75 mg, dexketoprofen 25 mg, tramadol 100 mg or placebo), according to a 3:3:3:1:1:1 randomisation ratio. During the multiple-dose phase, patients assigned to active treatment remained on the same treatment arm while patients assigned to placebo were re-allocated to receive one of the three possible active treatments (dexketoprofen/tramadol 25 mg/75 mg, dexketoprofen 25 mg or tramadol 100 mg). Overall, patients received seven consecutive doses of study drug within a three-day period (DEX-TRA-04) or 13 consecutive doses within a five-day period (DEX-TRA-05). RM (metamizole 500 mg, with a maximum recommended daily dose of 2 g) was available on request during the entire treatment period.

Following treatment administration, patients were requested to make multiple assessments of PI (at rest and on movement) and of PAR on an e-Diary over a period of three or five days, with the last assessment to be recorded eight hours after the last dose of study drug. Patients also had to make an overall assessment of the study medication (PGE) at the end of each study phase. The amount and the time when RM was used were also recorded. For both studies, the primary efficacy endpoint was the mean SPID at rest over eight hours after the first dose (SPID8).

The safety evaluation was based on the incidence of AEs, which were assessed throughout the entire study. Furthermore, safety was also evaluated by the assessment of clinically significant changes post-dose versus baseline in physical examination, vital signs, 12-lead ECG and laboratory safety tests (haematology, biochemistry and urinalysis).

DEX-TRA-04: the abdominal hysterectomy pain model

Demography and baseline characteristics of the different treatment groups were comparable. The overall mean age was 48 years (range 25 to 73 years). Initial pain was moderate in 38% patients and severe in 62% patients.

The results of the primary analysis (mean SPID8, Figure 2) confirmed the superiority of DKP.TRIS/TRAM.HCl over the single components (mean [SD]: 242 [139] for DKP.TRIS/TRAM.HCl versus 185 [139] for DKP.TRIS and 157 [151] for TRAM.HCl; p<0.001 for both comparisons). In addition, the comparisons of dexketoprofen and tramadol versus placebo (117 [122]) were both statistically significant (p<0.001 and p=0.010, respectively), confirming model sensitivity. Analyses on the per-protocol (PP) population confirmed the primary efficacy results.

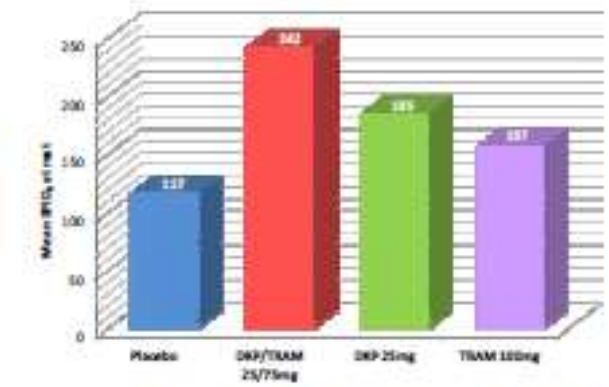


Figure 2 - Mean $SPID_8$ (Primary Endpoint). PI measured on a 0-100 VAS, with the left end labeled "no pain" and the right end labeled "worst possible pain".

There was statistical evidence favouring DKP.TRIS/TRAM.HCl over the single agents for all PI variables (mean PI, mean SPID, mean %max SPID and response to treatment) at rest during the single dose phase of the study. Superiority of DKP.TRIS/TRAM.HCl over the single agents was also seen for all PI variables at rest and on movement during the multiple-dose phase of the study. However, for mean PI (at rest and on movement) and for mean SPID on movement statistical significance was only achieved over dexketoprofen.

Statistically significant superiority of DKP.TRIS/TRAM.HCl over the single agents was shown for the PAR endpoints (mean PAR, mean TOTPAR and response to treatment) over 4, 6, and 8 hours.
There was evidence of a longer overall time to first use of RM on DKP.TRIS/TRAM.HCl compared to the single agents. The DKP.TRIS/TRAM.HCl combination was found to be superior to the single agents with regards to the time to use of RM during the single-dose. The percentage of patients using RM over 24 hours during the multiple-dose phase was statistically significantly lower with DKP.TRIS/TRAM.HCl than with the single agents. Results were maintained over 48 hours and overall during the multiple-dose phase, but the differences did not reach statistical significance. Overall, DKP.TRIS/TRAM.HCl was found to be statistically significantly superior to both single agents in terms of PGE scores for the single-dose phase, whereas the superiority was not maintained for the multiple dose phase of the study.

Overall, 76 (13%) patients reported a total of 100 ADRs, of which 51 were mild, 42 were moderate and 7 were severe. The most frequent ADRs (≥2% amongst the treatment group) were nausea (4.6% patients; 29 events), vomiting (2.3% patients; 14 events), abdominal distension (1.5% patients; 9 events), platelet count increased (1.3% patients; 8 events) and blood lactate dehydrogenase increased (1.0% patients; 6 events). The DKP.TRIS/TRAM.HCl group presented a lower incidence of ADRs (9.4% patients) in comparison with the DKP.TRIS (15% patients) and TRAM.HCl groups (13% patients). Overall, 11 (1.8%) patients reported a total of 15 serious adverse events (SAEs), of which only 1 (psychotic disorder; in the DKP.TRIS/TRAM.HCl group) was considered to be treatment-related. There were no marked differences between treatment groups in terms of safety outcomes, including vital signs, physical examination, 12-lead ECG or laboratory safety parameters. It was concluded that the study treatments were safe and well tolerated and that the DKP.TRIS/TRAM.HCl combination showed a safety profile fully in line with that previously known for the single agents.

DEX-TRA-05: the hip arthroplasty pain model

Demography and baseline characteristics of the different treatment groups were comparable. The overall mean age was 62 years (range 29 to 80). Baseline pain was moderate in 51% patients and severe in 49% patients.

For the primary endpoint (mean SPID8, Figure 3), the highest mean (SD) value was reported in the dexketoprofen/tramadol group [247 (157)]; values reported by dexketoprofen and tramadol groups were very similar, [209 (155)] and [205 (146)], respectively, and the lowest value was reported in the placebo group [151 (159)]. The combination was significantly better than dexketoprofen [p=0.019; 95% confidence interval (CI): 6.4 to 73] and tramadol (p=0.012; 95% CI: 9.5 to 76). In addition, both single agents were superior to placebo (p<0.05), thus confirming model sensitivity. Analyses on the PP population showed generally similar results, although the differences between dexketoprofen/tramadol and both single components were slightly inferior to those observed in the ITT population and did not reach statistical significance at the 5% level.

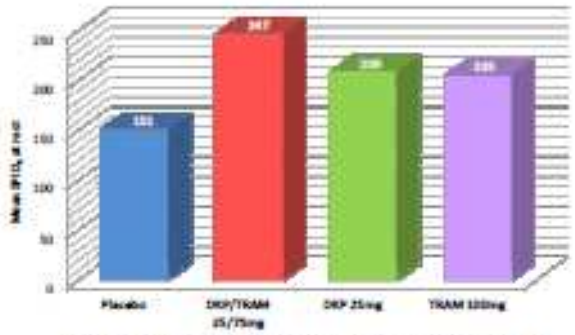


Figure 3 - Mean SPID$_8$ (Primary Endpoint). PI measured on a 0-100 VAS, with the left end labeled "no pain" and the right end labeled "worst possible pain".

When assessed by PI (mean PI, mean SPID, mean % max SPID, response to treatment), DKP.TRIS/TRAM.HCl was more effective than either DKP.TRIS monotherapy or TRAM.HCl monotherapy during both the single- and multiple-dose phases of the study. Superiority was generally established after the 2-hour time point following the first dose.

The highest mean TOTPAR and percentage of responders with regards to PAR during the single-dose phase were reported in DKP.TRIS/TRAM.HCl group when compared to the single agents, although the differences did not reach statistical significance. Similarly, the highest PGE scores were reported in the DKP.TRIS/TRAM.HCl group during the single- and multiple-dose phases of the study; however, no statistically significant differences were observed in comparison to the single components.

There was evidence of a longer overall time to first use of RM for DKP.TRIS/TRAM.HCl compared with DKP.TRIS monotherapy and TRAM.HCl monotherapy. In terms of percentage of patients using RM, the fixed dose combination was also found to be superior to both single components over 24 and 48 hours and overall during the multiple dose phase. The percentage of patients using RM over 24 and 48 hours and overall during the multiple-dose phase, were statistically significantly lower in the DKP.TRIS/TRAM.HCl group than in the DKP.TRIS group and in the TRAM.HCl group. The worst pain score whilst moving was slightly lower on average for the DKP.TRIS/TRAM.HCl group than for the DKP.TRIS group and the TRAM.HCl group on Day 2 and Day 3 during the multiple dose phase.

Overall, 27 (4.2%) patients experienced a total of 39 ADRs during the active treatment, of which 16 were mild, 18 were moderate and five were severe. The most frequent ADRs (≥1% amongst the treatment group) were nausea (0.9% patients; 6 events) and vomiting (0.6% patients; four events). The DKP.TRIS/TRAM.HCl group presented a lower incidence of ADRs (2.8% patients) in comparison with the DKP.TRIS group (4.7% patients) and the TRAM.HCl group (5.1% patients). Two patients reported a total of five serious ADRs. One patient in the DKP.TRIS group experienced duodenal ulcer. Another patient in the DKP.TRIS/TRAM.HCl group experienced periorbital oedema, face oedema, laryngeal oedema and haematuria. These events were resolved on the same day (haematuria resolved within two days). There were no marked differences between treatment groups in terms of safety outcomes, including heart rate, blood pressure, physical examination, 12-lead ECG, or laboratory safety parameters.

In summary, the results from the Phase III studies provided robust evidence of the efficacy of the DKP.TRIS/TRAM.HCl 25 mg/75 mg fixed-dose combination in the management of moderate to severe acute pain, as confirmed by the single dose efficacy, the repeated-dose sustained effect, and the good safety profile observed.

Phase IIIB study: DEX-TRA06 (dental pain model)

This was a multicentre, randomised, double-blind, double-dummy, parallel-group, placebo and active-controlled, single-dose, Phase IIIb study aimed to evaluate the analgesic efficacy, safety and tolerability of DKP.TRIS/TRAM.HCl 25 mg/75 mg in comparison with TRAM.HCl/paracetamol

75 mg/650 mg, in moderate to severe pain following surgical removal of impacted lower third molar. Participation in the study lasted for approximately 3 weeks for each patient and was made up of: a screening period, (within 2 weeks before randomisation), including the pre-surgery procedures to be completed at least 1 day prior to surgery and ending within the 4 hours qualification post-surgery; randomisation and treatment administration (day 1, t0) followed by an 8-hour assessment period during which patients recorded efficacy data followed by an end of study visit (6±1 days after randomisation).

Healthy adult patients (>18 years of age) scheduled for surgical extraction of at least one fully/partially impacted lower third molar requiring bone manipulation. A total of 654 patients were randomised and 653 were eligible for analysis. Surgery was performed under local anaesthetic using 2% lidocaine (with 1:80.000 epinephrine) up to a total volume of 5.4 mL per molar. No sedation was permitted.

Patients rated PI using an 11-point NRS (0 no pain; 10 worst pain). Participants experiencing moderate/severe pain (≥4) within 4 hours of surgery were randomised (2:2:1 ratio) to a single oral dose of TRAM.HCL/DKP.TRIS 75/25 mg, TRAM.HCL/paracetamol 75/650 mg or placebo.

Analgesia and pain were recorded by using the following measures: PAR on a 5-point VRS (0='no relief', 1='a little (perceptible) relief', 2='some (meaningful) relief', 3='lot of relief', 4='complete relief') at the predefined postdose time points t15 min, t30 min, t1 hour, t1.5 hour, t2 hour, t4 hour, t6 hour and t8 hour and PI on the 11-point NRS at t0 and at the same predefined postdose time points. The primary efficacy endpoint was TOTPAR, calculated as the weighted sum of the PAR scores measured according to a 5-point VRS, over 6 hours postdose (TOTPAR6).

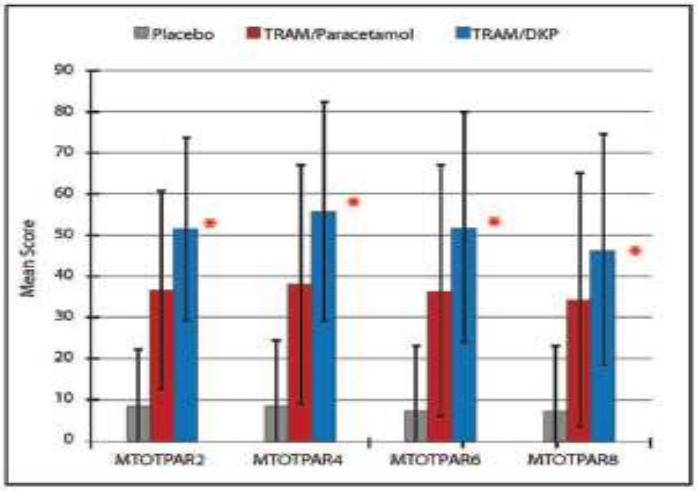


Figure 5 Percentage of max TOTPAR at 2, 4, 6 and 8 hours for TRAM/DKP, TRAM/paracetamol and placebo with PAR measured on a 5-point Verbal Rating Scale (0='no relief' to 4='complete relief'). *Statistically significant TRAM/DKP versus TRAM/paracetamol (p<0.0001). PAR, pain relief; TRAM/DKP, tramadol/dexketoprofen; TOTPAR, total pain relief.

The primary efficacy variable was analysed on the PP and ITT populations to assess the non-inferiority hypothesis. Since non-inferiority was confirmed, the ITT population was used to perform superiority analyses on the primary endpoint, as prespecified. The mean (SD) TOTPAR6 reported by patients in the TRAM.HCL/DKP.TRIS group was 13 (7.0), while those in TRAM.HCL/paracetamol and placebo groups were 9.2 (7.7) and 1.9 (3.9), respectively, demonstrating that the combination TRAM.HCL/DKP.TRIS was statistically superior (p<0.0001) to TRAM/paracetamol.

Secondary efficacy endpoints included the time course of mean PAR and PI scores over 8 hours; TOTPAR over 2, 4, and 8 hours postdose and the percentage of maximum calculated TOTPAR (% max TOTPAR) over 2, 4, 6, and 8 hours; sum of pain intensity difference (SPID) and the percentage of maximum calculated SPID (% max SPID) over 2, 4, 6, and 8 hours; percentage of responders in terms of PAR or PI reduction, namely subjects who achieved at least 50% of max TOTPAR or at least 30% of PI reduction versus baseline at prespecified time points over the 8 hours, respectively; time to FPPAR; time to confirmed FPPAR (ie, time to FPPAR if confirmed by experiencing MPAR) and time to MPAR; percentage of patients who achieved FPPAR, confirmed

FPPAR and MPAR within 30 min, 1 hour and 2 hours; PGE at 8 hours or whenever the patient used RM; time of first intake of RM since study drug intake; percentage of patients using RM at 2, 4, 6, or 8 hours.

Superiority of TRAM.HCL/DKP.TRIS overactive comparator and placebo was observed at all secondary endpoints. Overall, 53 patients (8.1%) experienced one or more ADRs (97 ADRs in total) but none of the ADRs were considered to be serious. No clinically relevant differences were identified in ADRs incidences between treatment groups. Overall, the most common ADRs were vomiting (3.8%), nausea (3.4%), dizziness (2.9%) and somnolence (2.1%). No deaths or other significant ADRs occurred. There were no clinically relevant changes in the vital signs or physical examination versus baseline.

Overall, the study confirmed that TRAM HCL/ DKP TRIS 75/25 mg oral fixed combination is effective and superior over TRAM HCL/paracetamol 75/650 mg in relieving moderate to severe acute pain following removal of impacted lower third molar. TRAM HCL/DKP TRIS 75/25 mg oral fixed combination shows faster onset of effect, greater and durable analgesia, together with a favourable safety profile.

DKP.TRIS/TRAM.HCl has already been compared to TRAM100 mg in several pain models (dental pain, abdominal laparotomic hysterectomy, and total hip arthroplasty) in order to evaluate DKP.TRIS/TRAM.HCl efficacy versus single agents (even at higher doses) in both visceral and somatic nociceptive pain.[27,28]

The aim of this study is to investigate the efficacy of DKP.TRIS/TRAM.HCl in moderate to severe acute LBP.

5.3 Assessment of Potential Risks and Benefits

The use of the 2 drugs in combination is well established in the medical practice as a part of the therapeutic armamentarium in the field of analgesia. Moreover, it is worthy of note that these data excluded hospital prescriptions, thus underestimating the real extent of use of the combination.

Overall, available data indicate that co-dispensation of DKP.TRIS and TRAM.HCl is part of current clinical practice.

Most of the patients in this study may derive a direct benefit from being treated with DKP.TRIS/TRAM.HCl, which has already demonstrated favorable efficacy at the doses tested. All participants taking part in the study may derive general medical benefit from careful and close monitoring by medical personnel during the study. Safety will be ensured by assessing participants for AEs and laboratory test results.

The inclusion of the single agents as active comparators has been deemed necessary in agreement with the Guideline on Clinical Development of Fixed Combination Medicinal Products (CPMP/EWP/240/95).[29] A placebo-controlled design has been selected for the single-dose phase (the first 8 hours after randomization) of the study, in agreement with both the Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain (CPMP/EWP/612/00)[30] and Guideline on Clinical Medicinal Products Intended for the Treatment of Neuropathic Pain (CPMP/EWP/252/03)[31] taking into account that the primary efficacy endpoint is evaluated in this period. The inclusion of the placebo arm during the single-dose phase is considered acceptable from an ethical point of view, considering the availability of RM and the fact that the use of placebo is limited to the first dose intake. After the first administration of study medication, placebo-assigned patients will be allocated to receive an active treatment such as TRAM.HCl 100 or DKP.TRIS/TRAM.HCl 25/75 mg. (see Section 7)

The placebo arm is included in the study to demonstrate analgesic effect of DKP.TRIS/TRAM.HCl compared with placebo as the primary objective. The patients assigned to the placebo arm will receive only one dose of placebo in the single-dose phase. These patients will later receive either DKP.TRIS/TRAM.HCl or TRAM.HCl in the multiple-dose phase. The availability of RM allows patients to take RM if they have not achieved adequate pain relief after receiving the assigned study drug. Paracetamol (acetaminophen) has been chosen as a RM as it is a safe and effective drug for the treatment of acute LBP, in addition it does not have interactions with the study medications.[32,33,34]

The most commonly observed AEs associated with DKP.TRIS are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea, vomiting, diarrhea, flatulence, constipation, dyspepsia, abdominal pain, melena, hematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed.

The most commonly reported ADRs associated with TRAM.HCl are nausea and dizziness, both occurring in more than 10% of patients. In the completed clinical studies performed with DKP.TRIS/TRAM.HCl, the most commonly observed ADRs were vomiting, nausea and dizziness (2.9%, 2.7%, and 1.1% of patients, respectively).

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

6. TRIAL OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
PRIMARY		
To evaluate the analgesic efficacy of DKP.TRIS/TRAM.HCl fixed combination versus placebo in moderate to severe acute low back pain after the first dose (first 8 hours).	Endpoints of primary interest: • Time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose (t8h). Other endpoints: Pain Relief (PAR)- VRS scores at each prespecified time point (t15m, t30m, t1h, t1.5h, t2h, t4h, t6h, t8h) over the 8 hours after the first dose. • Mean TOTPAR at 4, 6, and 8 hours (TOTPAR4, TOTPAR6, TOTPAR8) after the first dose. • Percentage of maximum TOTPAR (% max TOTPAR) at 4, 6, and 8 hours after the first dose.	The NRS is widely used clinically for the assessment of pain. This scale is a valid and reliable scale to measure pain intensity. High test-retest reliability has been observed for NRS in all kinds of patients. Efficacy endpoints of PAR, TOTPAR, SIPD, and PGE are well characterized and accepted endpoints both in the literature and by Regulatory authorities for evaluation of the analgesic

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	• Percentage of patients achieving at least 50% of maximum TOTPAR at 4, 6, and 8 hours after the first dose. • Mean Pain Intensity (PI) - VAS scores at each prespecified time points (t15m, t30m, t1h, t1.5h, t2h, t4h, t6h, t8h) over the 8 hours after the first dose. • SPID at 4, 6, and 8 hours (SPID4, SPID6, SPID8) after the first dose. • Percentage of maximum SPID (% max SPID) at 4, 6, and 8 hours after the first dose. • Percentage of patients achieving at least 30% of PI reduction versus baseline at 4, 6, and 8 hours after the first dose. • PGE of the study medication at 8 hours after the first dose. • Time to RM: Time elapsed between treatment administration and the first dose of RM from baseline till 8 hours after the first dose. • Percentage of patients who required RM within the first 4, 6, or 8 hours after the first dose.	benefits of investigational medications.
SECONDARY		
To evaluate the analgesic efficacy of DKP.TRIS/TRAM.HCl fixed combination versus TRAM.HCL 100 mg in moderate to severe acute low back pain after the first dose (first 8 hours).	• Same endpoints related to the single-dose phase as included for the primary objective will also be used to evaluate the analgesic efficacy of DKP.TRIS/TRAM.HCl versus TRAM.HCL in moderate to severe acute low back pain after the first dose (first 8 hours)	
To evaluate the analgesic efficacy of DKP.TRIS/TRAM.HCl fixed combination in moderate to severe	Endpoints of primary interest: • TOTPAR at 24 and 48 hours (TOTPAR24, TOTPAR48) of the multiple-dose phase.	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
acute low back pain versus TRAM.HCl 100 mg after multiple doses (from t8h until Day 5).	Other endpoints: • Pain Relief (PAR)-VRS scores at each prespecified time point over the multiple-dose phase. • TOTPAR at 72, and 96 hours (TOTPAR72, TOTPAR96) of the multiple-dose phase. • Percentage of maximum TOTPAR (% max TOTPAR) at 24, 48, 72, and 96 hours of the multiple-dose phase. • Percentage of patients achieving at least 50% of maximum TOTPAR at 24, 48, 72, and 96 hours of the multiple-dose phase. • Pain Intensity (PI)-VAS scores at each prespecified time point over the multiple-dose phase. • SPID at 24, 48, 72, and 96 hours (SPID24, SPID48, SPID72, SPID96) of the multiple-dose phase. • Percentage of maximum SPID (% max SPID) at 24, 48, 72, and 96 hours of the multiple-dose phase. • Percentage of patients achieving at least 30% of PI reduction versus baseline at 24, 48, 72, and 96 hours of the multiple-dose phase. • PGE at 96 hours of the multiple-dose phase. • Percentage of patients who required RM at 24, 48, 72, and 96 hours of the multiple-dose phase. • Roland Morris Disability Questionnaire at 96 hours of the multiple-dose phase. • Treatment Satisfaction Questionnaire for Medication at 96 hours of the multiple-dose phase. • Time to first achieve an NRS score <4 or a pain intensity reduction of ≥30% from the first drug intake till 5 days posttreatment, excluding patients	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	assigned to the placebo treatment arms during the single-dose phase. • TOTPAR at 104 hours from the first drug intake till 5 days after the first dose (TOTPAR104), excluding patients assigned to the placebo treatment arms during the single-dose phase. • SPID at 104 hours from the first drug intake till 5 days after the first dose (SPID104), excluding patients assigned to the placebo treatment arms during the single-dose phase. • Time to RM: Time elapsed between the first drug intake till 5 days after the first dose, excluding patients assigned to the placebo treatment arms during the single-dose phase.	
To assess the safety and tolerability of DKP.TRIS/TRAM.HCl fixed combination after single and multiple doses.	• Incidence, intensity (severity), seriousness and treatment causality of treatment-emergent AEs (TEAEs, reported starting from the study medication intake). • Frequency of clinically significant changes in clinical laboratory evaluations, physical examination, and vital signs post-dose versus baseline.	These are the most widely used endpoints for safety analysis.

7. STUDY DESIGN.

This is a Phase IV, multicenter, randomized, double-blind, double-dummy parallel group, placebo-controlled study encompassing 2 study phases: a single-dose phase (first 8 hours) and a multiple-dose phase starting after the single-dose phase (from t8 h until Day 5) aimed to investigate the efficacy of DKP.TRIS/TRAM.HCl fixed combination in moderate to severe acute LBP.

The study will be conducted in primary care and hospital setting in 6 European countries in 50-60 centers. The overall clinical phase is planned to start in Q3/2020 and to be completed within theQ2/2022.

Eligible patients will be randomized in a 4:4:1:1: ratio to 1 of the 4 possible treatment arms:

Arm	Single-dose phase (t0-t8)	Multiple-dose phase (t8-Day 5)
1	DKP.TRIS/TRAM.HCl	DKP.TRIS/TRAM.HCl
2	TRAM.HCl	TRAM.HCl
3	Placebo	DKP.TRIS/TRAM.HCl
4	Placebo	TRAM.HCl

In the single-dose phase the patients will receive a single dose treatment, consisting of 1 film-coated tablet and 2 capsules which must be orally administered together at the same time (Day 1) and according to Investigator's instructions. The multiple-dose phase will begin 8 hours after the first dose. The patients assigned to DKP.TRIS/TRAM.HCl fixed combination or TRAM.HCL 100 mg during the single-dose phase will continue to receive the same treatment during the multiple-dose phase; however, the patients assigned to receive placebo during the single-dose phase will either receive DKP.TRIS/TRAM.HCl fixed combination or TRAM.HCL 100 mg during the multiple-dose phase.
The study is considered completed when the last patient's last study visit has occurred.

7.1 Procedures and Study Visits

Patients will attend a total of 2 visits during the study. The description of the activities, procedures, and tests to be performed at each visit is detailed below.

1. **Visit 1 (Day 1, t0)**

The following procedures/assessments must be completed during the Screening:

- Obtaining informed consent.
- Patients will be asked to rate their PI on a paper to assess their eligibility for randomization. Patients must describe their PI in response to the question: 'How do you rate the intensity of your pain?' using an 11-point NRS ranging from 0 (no pain) to 10 (worst pain).
- Recording of prior and concomitant medications (CMs).
- Recording of medical history.
- Check of inclusion and exclusion criteria.
- Collection of demographic data.
- Physical examination including body weight, height and vital signs (blood pressure [BP], heart rate [HR]).

- Safety laboratory tests.
- Pregnancy test (if applicable).

Only patients experiencing pain of moderate or higher intensity (NRS score ≥5**)** and completing all screening procedures will be eligible for randomization. Randomization will be stratified according to:

- The baseline PI categories measured by the NRS scale in order to preserve the randomization ratio within each stratum:
  - ≥ 5 to ≤7 (moderate pain)
  - >7 (severe pain)
- The baseline radiculopathy categories measured by the Quebec Task Force classification35:
  - LBP without radiation
  - LBP+ radiation to extremity, proximally
  - LBP+ radiation to extremity, distally

Randomized patient will receive:

- E-diary and related instructions about its usage
- A box with Investigation Medicinal Products (IMP) and RM and instructions about its usage. It will be required to the patients to record the NRS-PI and VRS-PAR to e-Diary before RM intake.
- Instructions regarding how to complete the patient's pain and analgesia assessments.

A follow up phone call after Visit 1 will be performed within 24 hours from results only in case of abnormality and clinically relevant laboratory test according to the investigator judgement.

2. Complete treatment and Assessment Period (Day 1 to Day 5)

Treatment and assessment period consists of a single-dose phase (t0 to t8h) and a multiple-dose phase (t8h to Day 5). Prior to the administration of the study treatment the following items will be recorded as baseline PI (t0h):

- NRS-PI; patients with NRS score ≥5 at the Screening, who could have NRS <5 between the period of Screening and before the first dose intake, will be randomized.

- Roland Morris Disability Questionnaire (RMQ), patients will answer to 24 questions that enquire back pain on movement during daily life activities. The RMQ is a self-administered disability measure in which greater levels of disability are reflected by higher numbers on a 24-point scale. Each question is worth 1 point, so scores can range from 0 (no disability) to 24 (severe disability). Clinical improvement over time can be graded based on the analysis of serial questionnaire scores.

a. Single-dose phase (t0 – t8h)

- The single-dose phase corresponds to the first 8 hours after the first study treatment administration.
- The first dose should be taken by 16:00 on Day 1.
- After the first study treatment administration, patients will remain under observation at the site for 2 hours.
- The pain and analgesia assessments measured by NRS-PI and Verbal Rating Scale-Pain Relief (VRS-PAR) will be recorded by the patients on the e-Diary at t15min, t30min, t1h, t1.5h, t2h, at the clinical site, and at t4h, t6h and t8h and immediately before RM intake (if any) off the clinical site.
- Patient Global Evaluation (PGE): At the end of the single-dose phase (t8h), subjects will be asked to answer the question: “How would you rate the medication received for your pain?” using a 5-point VRS, where: 1= ‘poor’, 2 = ‘fair’, 3 = ‘good’, 4 = ‘very good’, 5 = ‘excellent’.
- First intake of RM, if any.
- Occurrence of any AE as spontaneous reporting and changes in CMs, if any, will be collected by study staff while the patients are at the site.

b. Multiple-dose phase (t8h- day5)

The multiple-dose phase will start on Day 1 with the second dose administration, when the single-dose phase is completed.

- Patients receiving DKP.TRIS/TRAM.HCl or TRAM.HCl during the first 8 hours will continue with the same treatment while patients who received placebo will switch to DKP.TRIS/TRAM.HCl or TRAM.HCl according to the randomization scheme specified above. During the multiple-dose

phase 12 doses of study treatment will be administered, with the last study drug intake administered within Day 5.

- The frequency of the dosing is 8 hours.
- During this phase, patients will continue recording the following items on their e-Diaries:
  - NRS-PI, immediately prior to each dose of study treatment and 2 hours after each dose every day, with the last assessment to be completed on Day 5, 8 hours after the last dose intake. Within this period the NRS-PI shall be done also immediately before RM is taken, if any.
  - VRS-PAR, immediately prior to each dose of study treatment and 2 hours after each dose every day, with the last assessment to be completed on Day 5, 8 hours after the last dose. Within this period, the VRS-PAR shall be done also immediately before RM is taken, if any.
  - The RMQ will be assessed on Day 5, 8 hours after the last dose or whenever patients discontinue treatment.
  - PGE will be assessed on Day 5, 8 hours after the last dose or whenever patients discontinue treatment.
  - Treatment Satisfaction Questionnaire for Medication (TSQM) will be assessed on Day 5, 8 hours after the last dose or whenever patients discontinue treatment. It is comprised of 14 questions that provide scores on 4 scales: effectiveness (3 items), side effects (5 items), convenience (3 items) and global satisfaction (3 items).
  - During the multiple-dose phase, the study team will record AEs on spontaneous reporting.

3. Visit 2: End of study (Day 6 +2 days)

- Return of e-Diary, unused IMP, unused RM and empty blisters by patients
- Physical examination
- Vital sign measurements
- Safety laboratory test
- Pregnancy test (if applicable)
- IMP accountability

- RM accountability
- Recording of AEs and changes in CM, if any, since the last visit

NOTE: For the study purposes, patients will be required to attend the study center to accomplish the procedures from Screening to End of study.

After the last dose intake on Day 5, the "follow-up period" will last until Visit 2 (Day 6 +2 days). A follow-up phone call after Visit 2 will be performed within 24 hours from results only in case of abnormality and clinically relevant laboratory test according to the investigator judgement.

8. SELECTION OF SUBJECTS

Informed Consent Process

Prior to the patient's enrolment into the study and before performing any study-related procedures, the Investigator - or its authorized delegate - shall obtain the patient's written, dated and signed informed consent to participate into the study and to the confidential disclosure, processing and transferring necessary documentation of the patient's health and personal data to the contract research organization (CRO), Sponsor and its Affiliates, the competent Health Authorities (HA) and any other institutions, as legally required and in accordance with the local applicable privacy laws (for the Privacy information to be reported on the informed consent form (ICF) refer to Section 19).

The institution and Investigator undertake to duly inform patients about personal data processing and the relevant applicable privacy rights before their participation in the study.

After being duly informed and interviewed by the Investigator, the patient freely has to date and sign the ICF before being enrolled into the study and before undergoing any study procedure. The Investigator must store the original of the signed ICF in the Investigator's File, and the patient will be provided with a copy of it. If a protocol amendment would affect the terms of the ICF, it will be revised to reflect the protocol change and submitted to the Ethics Committee (EC) for approval. The Investigator will ensure that this new consent form is signed by all patients subsequently entered in the study and those currently in the study, if affected by the amendment.

8.1 Inclusion and Exclusion Criteria

8.1.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Properly executed written informed consent.
2. Male or female patients aged 18 years to 65 years.
3. Patients with acute low back reporting pain of at least moderate intensity at Screening (NRS score ≥ 5). The onset of the current acute low back pain episode is within 48 hours prior to Screening.
4. Patients with or without radiculopathy will be included, excluding those with neurological signs, according to the Quebec Task Force classification.
5. Naïve patients to any low back pain or patients with previous history of low back pain experiencing a new episode, preceded by a period of at least 2 months without any low back pain prior to Screening.
6. Patients free from analgesic (as per exclusion criterion 15) due to previously administered pain killer (immediate or slow release formulations), according to physician's judgment.
7. Females participating in the study must be either:
   - Females of nonchildbearing potential, defined as any woman who had undergone surgical sterilization (documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or is more than 2 years postmenopausal (defined as no menses for 12 months);
   - Females of childbearing potential (following menarche until menopause unless permanently sterile) provided that they have a negative pregnancy test at Screening and are routinely using an effective method of birth control resulting in a low failure rate (ie, combined hormonal contraception, intrauterine device, condoms in combination with a spermicidal cream, male partner sterilization (vasectomy), bilateral tubal occlusion or total sexual abstinence) during the study treatment.
8. Mentally competent and able to understand and give written informed consent prior to Screening.
9. Compliant to undergo all visits and procedures scheduled in the Study.

8.1.2. Exclusion Criteria

1. Patients who are judged by the Investigator not to be suitable candidates for the study treatments and the RM based on their medical history, physical examination, CM and concurrent systemic diseases.
2. Clinically significant abnormalities in the vital signs as per Investigator's judgment.
3. Patients with acute low back pain and radiation to limb with presence of neurologic signs (focal weakness, asymmetry of reflexes, sensory loss in a dermatome, or loss of bowel, bladder, or sexual function, according to Quebec Task Force Classification).
4. History of hypersensitivity to the study treatments, RM or to any other NSAIDs, or opioids.
5. Known photoallergic or phototoxic reactions during treatment with ketoprofen or fibrates.
6. History of peptic ulcer, gastrointestinal disorders when taking NSAIDs, gastrointestinal bleeding, or other active bleeding.
7. History of allergy (eg, precipitate attacks of asthma, bronchospasm, acute rhinitis, or cause nasal polyps, urticaria or angioneurotic oedema) to the study treatments, RM or to any other NSAIDs, or opioids.
8. Anamnestic mild to severe renal dysfunction, mild to severe hepatic dysfunction, as per Investigator's judgment.
9. Patients with chronic dyspepsia.
10. Patients with severe heart failure (Class III and Class IV of New York Heart Association [NYHA] Classification).
11. History of hemorrhagic diathesis and other coagulation disorders.
12. History of or current epilepsy or convulsions.
13. Patients with Crohn's disease or ulcerative colitis.
14. Patients receiving monoamine oxidase (MAO) inhibitors (a minimum of 14 days of washout must elapse prior to the first study drug dose).
15. Treatment with topical preparations/medications within 4 hours prior to Screening, anesthetics and muscle relaxants within 8 hours prior to Screening, short-acting analgesics (eg, paracetamol) within 4 hours prior to Screening, other analgesics (NSAIDs [eg, ketoprofen, ibuprofen, diclofenac) within 5 half-lives prior to Screening, or use of an opioid within the 14 days preceding Screening.

16. Treatment with high doses of salicylates (≥3 g/day), anticoagulants, thrombolytic and antiplatelet agents, heparins, corticosteroids (except inhalers and topical agents), lithium methotrexate, used at high doses of 15 mg/week or more, hydantoins (including phenytoin) and sulphonamides, antiepileptics, antipsychotics, serotonin reuptake inhibitors (selective serotonin reuptake inhibitors [SSRIs] and serotonin norepinephrine reuptake inhibitors [SNRIs]) and tricyclic antidepressants, and analgesics within 48 hours or 5 half-lives (whichever is the longer) prior to Screening.
17. Patients using sedatives (eg, benzodiazepines) and hypnotic agents within 8 hours before Screening.
18. Any chronic or acute painful condition other than the study indication that may interfere with the assessment of the efficacy of the study treatment.
19. Any non-pharmacological interventional therapy for low back pain (physical therapy, acupuncture, massage etc.) one month before Screening.
20. Patients with litigation related to work.
21. Patients with severe dehydration (caused by vomiting, diarrhea, or insufficient fluid intake) within one month prior to Screening.
22. Severe respiratory depression according to physician's judgment.
23. Participation in other clinical studies in the previous 4 weeks.
24. History of drug or alcohol abuse. For the purpose of the study, alcohol abuse is defined as regularly intake of more than 4 units of alcohol per day (1 unit corresponds approximately to 125 mL wine, 200 mL beer, 25 mL spirit).
25. History of any illness or condition that, in the opinion of the Investigator might pose a risk to the patient or confound the efficacy and safety results of the study.
26. Pregnant and breastfeeding women. NOTE: a pregnancy test will be performed on all women of childbearing potential at Screening.
27. Patients presenting any of the contraindications reported for dexketoprofen/tramadol, tramadol or paracetamol (according to the SmPC).
28. Known or suspected serious spinal pathology (eg, metastatic, inflammatory or infective diseases of the spine, cauda equine syndrome, trauma, spinal fracture).
29. Spinal surgery within the preceding 6 months.

8.1.3. Screening Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently entered in the study or assigned to the study product. The screen failures will not be continued in the study and re-screening is not allowed.

9. STUDY TREATMENT

The treatments administered during the study are:

Dexketoprofen Trometamol/Tramadol Hydrochloride

DKP.TRIS 25 mg/TRAM.HCl 75 mg film-coated tablets (as one film-coated tablet)

Reference Therapy:

- Placebo film-coated tablets matching DKP.TRIS 25 mg/TRAM.HCl 75 mg
- Placebo capsules matching active comparator TRAM.HCl 100 mg (as 2 capsules of Tramadol 50 mg)

Active Comparator:

TRAM.HCl 100 mg (as 2 capsules of Tramadol 50 mg)

Dosage form of the treatments:

Oral tablets and capsules.

Regimen: every 8 hours, with maximum 13 consecutive doses within a 5-day period.

- Double-dummy technique will be applied to ensure double-blind condition of DKP.TRIS 25 mg/TRAM.HCl 75 mg versus TRAM.HCl 100 mg versus placebo administration.

Individual study participation will last up to 8 days for each treatment group. For further details on the study design, please see Section 7.1.

Treatments administered - posology schedule and duration

Single-dose phase:

The patients who are eligible will be randomly allocated to 1 of the 4 treatment groups.

Patients will receive 1 of the 4 possible treatments:

- DKP.TRIS 25 mg/TRAM.HCl 75 mg, as one film-coated tablet
- TRAM.HCl 100 mg, as two capsules with 50 mg each
- Placebo, as one film-coated tablet matching DKP.TRIS 25 mg/TRAM.HCl 75 mg
- Placebo as two capsules matching TRAM.HCl

One single dose treatment, consisting of 1 film-coated tablet and 2 capsules, has to be orally administered together at the same time (Day 1) and according to Investigator's instructions.

Multiple-dose phase:
Patients assigned to placebo treatment in the single-dose phase, will be allocated to receive 1 of the 2 possible study active treatments, every 8 hours:

- DKP.TRIS 25 mg/TRAM.HCl 75 mg, as one film-coated tablet
- TRAM.HCl 100 mg, as two capsules with 50 mg each

Conversely, patients who are already assigned to active treatment in the single-dose phase, will remain on the same active treatment.

Multiple-dose treatment, each dose consisting of 1 film-coated tablet and 2 capsules, has to be orally administered together, every 8 hours, up to the end of Day 5, for a total of 12 drug administrations and according to Investigator's instructions.

9.1 Study Treatment Formulation, Appearance, Packaging, and Labeling

IMP Manufacturing:
Placebo film-coated tablets matching DKP.TRIS 25 mg/TRAM.HCl 75 mg will be manufactured by A. Menarini Research & Business Service GmbH (Menarini Group), Glienicker Weg 125, 12489 Berlin, Germany.
Placebo capsule matching active comparator Tramadol 50 mg will be manufactured by A. Menarini Manufacturing Logistics and Services S.R,L., (Menarini Group), Via Sette Santi, 3 50131- Florence (Italy).

DKP.TRIS 25 mg/TRAM.HCl 75 mg film-coated tablets and TRAM.HCl 50 mg capsules will be sourced as authorized EU marketed products from commercial supplier in the European market.

Packaging and Labelling:
The packaging and labelling of IMP will be performed by A. Menarini Manufacturing Logistics and Services S.R,L., (Menarini Group), Via Sette Santi, 3 50131- Florence (Italy).
All the IMPs will be provided in dedicated treatment boxes (Patient Box) to be dispensed at Day 1, upon randomization. The IMP will be packaged as described below:

IMP Primary packaging:

PVC/PVDC//Aluminum blister.

Each blister contains 1 (one) film-coated tablet or 2 (two) capsules, corresponding to randomized treatment.

For each dose, patient must be instructed to intake together at the same time 1 (one) film-coated tablet and 2 (two) capsules, corresponding to dose of the randomized treatment.

IMP Secondary packaging:

One blister (containing 1 film-coated tablet) and 1 (one) blister (containing 2 capsules), corresponding to randomized treatment, will be packaged together in the same one labelled box.

Each Patient Box will contain 15 labelled boxes (1 labelled box for the single-dose phase; 12 labelled boxes for the multiple-dose phase and 2 labelled boxes as “spare” doses).

IMP Patient Box Secondary packaging:

Each Patient box will contain 15 film-coated tablets (15 blisters) and 30 capsules (15 blisters), which suffice for a total of 13 treatment doses of the randomized treatment and 2 “spare” doses.

IMP Labelling:

The IMP will be labelled in compliance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines, as well as any additional national requirement, and standard operating procedures (SOPs).

The label content will be in local language for each country and will report the contents of the boxes and the instructions how to administer and store the IMP.

Rescue Medication (RM):

Paracetamol 500 mg tablets, oral administration.

Paracetamol 500 mg tablets will be sourced from EU countries and as commercial product from authorized suppliers.

Rescue medication will be provided in the same commercial primary packaging (blister with 10 tablets).

Commercial blisters will be repackaged only in dedicated boxes (2 blister/box) and labelled.

Rescue medication will be supplied to patients together the IMP in the same Patient box: each Patient Box will contain 1 RM box with 20 tablets (2 blister x 10 tablets).

All repackaging and labelling operations will be performed by A. Menarini Manufacturing Logistics and Services S.R,L., (Menarini Group), Via Sette Santi, 3 50131- Florence (Italy).

The label content will be in local language and will report the contents of the RM boxes and the instructions how to administer and store the RM.

9.2 Study Treatment Distribution and Return/Destruction

Drug accountability:

The Principal Investigator of each participating institution will be responsible for the management of all IMP/RM to be used for the clinical trial.

An inventory will be maintained by the Principal Investigator (or designee) to include a signed account of all IMP/RM received, dispensed to and returned by each patient at the planned visits.

An explanation will be given for any discrepancies.

At the conclusion of the study, the Drug Accountability Form will be completed after a final IMP/RM supply inventory.

Drug return:

All used or unused IMP/RM must be returned, on agreed conditions, defined by the Sponsor.

All used or unused IMPs must be accounted for and provided with relative return documentation duly filled in, signed and dated as appropriate. Any discrepancy (if any) must be investigated and satisfactorily explained.

Drug destruction:

Destruction of all IMP/RM (used or unused) will be carried out after written authorization of the Sponsor.

9.3 Product Storage and Stability

The IMPs and rescue medication should be stored in the original packaging at a temperature below 25°C, in a secure area, protected from light, and inaccessible to unauthorized personnel.

9.4 Study Product Compliance

Treatment compliance will be monitored from Visit 1 to end of study treatment. The Principal Investigator must instruct patients to return to clinical site IMP Patient box received. The amount of IMP/RM taken by the patient will be derived by counting the number of tablets/capsules in the blister returned and it will be recorded in the electronic case report form (eCRF).

The patient compliance for study treatment period is calculated by the following formula: % compliance = number of tablets/capsules actually taken x 100 / expected number of tablets/capsules which should have been taken.

$$Compliance\ (\%) = \frac{units\ of\ tablets/capsules\ \ actually\ taken}{units\ of\ tablets/capsules\ expected\ \ to\ be\ taken} \cdot 100$$

The overall patient compliance will be calculated as the percentage of the number of tablets/capsules actually taken by the patient over the number of tablets/capsules expected to be taken.
The number of tablets/capsules actually taken will be calculated as the difference between the number of tablets/capsules handled out to the patient and the number of unused tablets/capsules returned or declared lost by the patient.

The expected number of total tablets/capsules taken for each patient will be 39 based on 13 (thirteen) administrations with 3 tablets/capsules per administration.
A patient who has taken at least 80% and no more than 120% of the required IMPs intake since the last visit will be considered compliant

9.5 Concomitant Therapy/ies

Any medication that the patient is receiving at the time of enrolment and the regular and occasional use of any CM during the study is to be recorded on the eCRF. If additional analgesia is needed during the treatment and assessment period, patients should take only the provided RM.

9.6 Not Permitted Medications

The following drugs are prohibited according to the timeline provided and up to 24 hours after last intake of study medication:

- Treatment with topical preparations/medications within 4 hours prior to Screening, anesthetics and muscle relaxants within 8 hours prior to Screening, short-acting analgesics (eg, paracetamol) within 4 hours prior to Screening (NSAIDs [eg, ketoprofen, ibuprofen, diclofenac]), other analgesics within 5 half-lives prior to Screening, and use of an opioid within the 14 days preceding Screening
- Any non-pharmacological therapy for low back pain (physical therapy, acupuncture, massage etc.) one month before Screening
- Sedatives (eg, benzodiazepines) and hypnotic agents within 8 hours before Screening

The following drugs are prohibited within 48 hours or 5 half-lives (whichever is the longer) prior to the Screening and up to 24 hours after last intake of study medication:

- High doses of salicylates (≥3 g/day)
- Anticoagulants, thrombolytic, and antiplatelet agents
- Heparins
- Corticosteroids (except inhalers and topical agents)
- Lithium
- Methotrexate used at high doses of 15 mg/week or more
- Hydantoins (including phenytoin) and sulphonamides
- Monoamine oxidase (MAO) inhibitors in the 14 days prior to the use of the opioid.
- Antiepileptics
- Antipsychotics
- Serotonin reuptake inhibitors (SSRIs and SNRIs) and tricyclic antidepressants

9.7 Rescue Medicine

Rescue medication can be taken at any time after the first dose if adequate pain relief is not achieved with the study treatment. However, the patients will be encouraged to wait for at least 60 minutes after dosing to allow time for the study treatment effect to take place. Paracetamol 500 mg for a maximum of 2 g per day is the recommended rescue medication. Patients will be duly instructed by the Investigator regarding the proper posology and method of administration and will be also instructed to bring back the remaining RM at Visit 2. The patients will be instructed to fill the RM accountability in e-Dairy appropriately to avoid overdosing and to control the RM intake.

10. STUDY ASSESSMENT AND PROCEDURES

10.1 Assessment of Efficacy

The efficacy parameters will be used to test both the superiority of DKP.TRIS/TRAM.HCl versus placebo and the noninferiority of DKP.TRIS/TRAM.HCl when compared to TRAM.HCl. The following efficacy parameters will be used to assess the efficacy of the study treatment in the study:

Numerical Rating Scale - Pain Intensity (NRS-PI)

The NRS-PI is a 11-point rating scale to assess the pain intensity. The patients will be asked to rate their PI in response to the question: 'How do you rate the intensity of your pain?' ranging from 0 (no pain) to 10 (worst pain). Based on the rating scale, PI scores will be calculated at each pre-specified time points. The summed pain intensity difference (SPID [SPID24, SPID48, SPID72, SPID96]), percentage of maximum SPID (% max SPID) and percentages of patients achieving at least 30% of PI reduction versus baseline will be calculated at 4, 6, and 8 hours after first dose in the single-dose phase and 24, 48, 72, and 96 hours after the first dose of the multiple-dose phase of the study.

Verbal Rating Scale - Pain Relief

The VRS is a 5-point verbal rating scale to assess the pain relief. In this assessment, the patients will be asked to answer the question 'How do you rate your pain relief?', where 0 = 'no relief', 1 = 'a little (perceptible) relief', 2 = 'some (meaningful) relief', 3 = 'lot of relief', 4 = 'complete relief'. Based on the rating scale, pain relief (PAR) scores, total pain relief (TOTPAR), percentage of maximum TOTPAR (% max TOTPAR) and percentage of patients achieving at least 50% of maximum TOTPAR will be calculated at prespecified time point points in the single and multiple-dose phases of the study.

Roland Morris Disability Questionnaire (RMQ)

The RMQ is a self-administered disability measure in which greater levels of disability are reflected by higher numbers on a 24-point scale. Each question is worth 1 point, so scores can range from 0 (no disability) to 24 (severe disability). The patients will have to answer 24 questions that inquire about back pain on movement during daily life activities. Clinical improvement over time can be graded based on the analysis of serial questionnaire scores.

Patient Global Evaluation (PGE)

The PGE is a 5-point verbal rating scale where the patients will be asked to answer the question: 'How would you rate the medication received for your pain?' where 1= 'poor', 2 = 'fair', 3 = 'good', 4 = 'very good', 5 = 'excellent'. The PGE will be assessed 8 hours after the first dose and 96 hours after the multiple-dose phase or whenever patients discontinue treatment.

Treatment Satisfaction Questionnaire for Medication (TSQM)

The TSQM comprises of 14 questions that provide scores on 4 scales: effectiveness (3 items), side effects (5 items), convenience (3 items), and global satisfaction (3 items). This will be assessed on Day 5, 8 hours after the last dose or whenever patients discontinue treatment.

10.2 Assessment of Safety

Safety will be assessed through collection of treatment-emergent AEs that started after the first dose of study treatment (incidence, severity, seriousness, treatment causality), clinical laboratory test evaluation, and physical examination (body weight, height, vital signs, blood pressure, and heart rate). Safety assessments will be performed at time points as described in Section 4.1.

The following laboratory tests will be performed for evaluation of safety:

- Hematology: Red blood cell (RBC) count, hematocrit (HCT), hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet count, white blood cell (WBC) count, and differential WBC count (neutrophil, lymphocyte, monocyte, eosinophil and basophil count, absolute and %).
- Serum biochemistry: Sodium, potassium, chloride, total calcium, glucose, creatinine, urea, total protein, albumin, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), and creatine phosphokinase (CPK).

  Note: For patient who will discover an abnormal renal function (creatinine clearance ≤ 60 mL/min) and/or an abnormal hepatic function (Child-Pugh class A to C) will be terminated from treatment and study.
- Coagulation test (only at Screening): prothrombin time, partial thromboplastin time (PTT), INR.

- Urinalysis: Urinalysis will be performed using dipstick during the Screening and at the end of the study (Visit 2). The following parameters will be analyzed: specific gravity, pH, leucocytes, nitrite, protein, glucose, ketones, urobilinogen, bilirubin, blood (erythrocytes, hemoglobin).
- Pregnancy test: Pregnancy test, if appropriate, will be performed using stick pregnancy test during the Screening period and at the End of Study Visit.

All the laboratory evaluations will be performed in the central laboratory (Q Squared Solutions).

11. SAFETY DATA MANAGEMENT

11.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

11.2 Drug Relationship

The relationship between an AE and study drugs will be judged according to the following categories:

1. **Certain**: The AE occurs in a plausible time relation to the administration of the drug and cannot be explained by a concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
2. **Probable:** The AE occurs in a reasonable time relation to the administration of the drug, it is unlikely to be attributed to a concurrent disease or other drugs or chemicals and it follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information (AE reappearance after drug reintroduction) is not required to fulfil this definition.
3. **Possible**: The AE occurs with a reasonable time relation to the administration of the drug, but it could also be explained by a concurrent disease or other drugs or chemicals. Information on drug withdrawal (dechallenge) may be lacking or unclear.
4. **Unassessable:** The relationship cannot be judged, because of the information is insufficient or contradictory and cannot be supplemented or verified.

5. **Unlikely**: A causal relationship cannot be definitively ruled out, but
    - Other drugs, chemicals, or underlying disease provide plausible explanations and/or
    - The temporal relation to the administration of the drug makes a causal relation improbable.
6. **Not Related**: Any of the following are present:
    - existence of a clear alternative explanation, and/or
    - unreasonable temporal relationship between Drug and Event, and/or
    - non-plausibility.

11.3 Adverse Drug Reaction (ADR)

An ADR is any untoward and unintended response to an investigational medicinal product related to any dose administered.

The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

An ADR is considered any AE for which the relationship is considered as:

1. Certain
2. Probable
3. Possible
4. Unassessable.

An AE is not considered as an ADR when the relationship is judged as:

1. Unlikely
2. Not related.

11.4 Seriousness

An AE/ADR is considered serious when it:

1. Results in death;
2. Is life-threatening;

Note: Life-threatening is considered any AE in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

3. requires inpatient hospitalization or prolongation of existing hospitalization;
4. results in persistent or significant disability/incapacity;
5. is a congenital anomaly/birth defect;
6. is another medically important condition that may jeopardize the patient or may require intervention to prevent 1 of the outcomes listed above. Any suspected transmission of an infectious agent via a medicinal product is considered serious and should be assessed under the category of medically important events in the absence of other seriousness criteria.

An AE/ADR is considered Non-serious when it does not fulfill the conditions for the definition of Serious AE/ADR.

11.5 Adverse Event/Adverse Drug Reaction Intensity

The intensity level of a Serious or a Non-serious AE or ADR is attributed according to the following definitions:

- **Mild:** does not interfere with routine activities; in case of laboratory tests, when there is a mild abnormality.
- **Moderate**: interferes with the routine activities; in case of laboratory tests, when there is a moderate abnormality.
- **Severe**: makes it impossible to perform routine activities; in case of laboratory tests, when there is a significant abnormality.

11.6 Adverse Event/Adverse Drug Reaction Expectedness

An AE/ADR is considered Unexpected when the nature, severity, or outcome of the AE/ADR is not consistent with the information provided in the Reference Safety Document (Summary of Product Characteristics).

11.7 Serious Unexpected Adverse Drug Reaction (SUSAR)

Any SAE judged by the Investigator or the Sponsor as drug-related (see Section 11.3) and considered as unexpected qualifies as a SUSAR.

SUSARs are subject to expedited reporting, as specified in Section 11.10, as having a “Reasonable Possibility” of relationship with the IMP.

11.8 Individual Case Safety Report (ICSR)

Format and content provided to describe 1 or several AEs or a disease experience that occur to an individual patient at a particular point of time.

11.9 Collection, Recording and Reporting of AEs

At each visit the Investigator will collect and assess any occurred subjective or objective AE occurred to each patient after his/her signature of the informed consent.

The Investigator should manage as AE any laboratory test abnormality (newly occurring after the IMP administration or worsening of previously known abnormalities) considered as clinically relevant: ie, values significantly above or under normal range or which require an intervention or diagnostic tests or may result in the IMP discontinuation.

Any AE communicated by the patient or by the patient's relatives or delegates through phone calls, letters or e-mails will also be collected and assessed.

The Investigator shall record on the respective eCRF AE recording pages any recognized AE identifying an ICSR, both serious and non-serious, whether or not thought to be drug-related, observed in or reported by the patient (or relatives/delegates), specifying the judgement on the causal relationship with the study treatment.

Any available information and diagnostic measure (laboratory and instrumental tests, procedures, etc.) shall be recorded in and/or attached to the concerned eCRF pages/sections.
The Investigator is expected to record also any AE occurring during the study follow-up period (up to Visit 2) after the administration of the last treatment dose.

The Investigator is expected to follow-up any AE occurred during the study, including the follow-up period (period between the last drug intake and the visit 2), until the outcome of the AE has been determined.

The Investigator must report all the collected information on any ICSR with Serious and Nonserious AE (whether or not thought to be related to the investigational drug), providing the concerned eCRF-AE pages by alert e-mail, after the first knowledge of the occurrence of the case, to:

CRO Pharmacovigilance Officer: Vedran Stančić
E-mail : vedran.stancic@iqvia.com
Fax : NA
Mobile: +385 91 4171-128

When relevant, also the eCRF pages concerning medical history, CM, and laboratory tests will be placed at Sponsor disposal by e-mail.

11.10 Management of Serious AEs (SAEs) including laboratory abnormalities

- **Reporting Duties of the Investigator**

The Investigator must report all the collected information on any ICSR with SAE (whether or not thought to be related to the investigational drug), as above specified, no later than 24 hours after the first knowledge of the occurrence of the case.
Any further information and supporting documentation that become available (copies of laboratory reports, tests, procedures, autopsy evidence of the cause of death, etc.) shall be provided no later than 24 hours after the knowledge, by the Investigator to the CRO by alert e-mail, to be forwarded to the Sponsor.
The Investigator must also comply with the local applicable obligation(s) on the reporting of ADRs to the local concerned Regulatory Authority/EC.

- **Reporting Duties of the Sponsor**

The Sponsor shall ensure that all relevant information about any suspected serious and unexpected adverse drug reaction (SUSAR), is expeditiously reported to the competent Authorities (including EudraVigilance Clinical Trial Module for clinical trials for which a EudraCT number has been assigned) and ECs (following general and local rules and procedures), with these deadlines after the first knowledge, intended as the day when the CRO receives the notification of the SUSAR:

– Fatal and life-threatening unexpected cases, no later than 7 days;
– Other unexpected serious cases, no later than 15 days.

The Sponsor shall ensure that all relevant information and supporting documentation that subsequently becomes available, is also expeditiously reported as follow-up information according to the above-mentioned deadlines.

Since this study is blinded, the patient's code will be broken before the expedited reporting to the Competent Authorities and the ECs.

Furthermore, the following safety issues will be subjected to expedited management for the identification of possible necessary actions:

- SAEs associated with the study procedures
- Potential clinically significant findings emerging from non-clinical studies
- An anticipated end or suspension for safety reasons of another study with the same study drug.

When appropriate and applicable the Sponsor will arrange the adequate information also to the Investigators.

11.11 Management of Non-serious AEs (NSAEs) including laboratory abnormalities

- **Reporting Duties of the Investigator**

The Investigator must report all the collected information on any ICSR with NSAE (whether or not thought to be related to the investigational drug), as above specified, no later than 5 Calendar days after the first knowledge of the occurrence of the case.

Any further information and supporting documentation that become available (copies of laboratory reports, tests, procedures, etc.) shall be provided **no later than 24 hours** after the knowledge, by the Investigator to the CRO by e-mail or fax to be forwarded to the Sponsor.

11.12 Management of any laboratory abnormality

Any laboratory test abnormality which is considered by the Investigator as AE is to be managed as above detailed (refer to Section 11.9).

However, all "out of range" values should be collected and reviewed periodically by the CRO medical team (medical data review team first reviews listings of laboratory values and send them to Therapeutic Medical Advisor for second review and approval). In case that the laboratory values deemed to be significant, but the site did not report or ignored them, MDR will raise query to the site in attempt to find appropriate answer. MDR will close the query after. On monthly basis all medical queries will be reviewed with the sponsor..

11.13 Management of pregnancy exposure cases

The Investigator is expected to record in the provided form any case of pregnancy exposure occurring in a female patient or in a male patient's partner during the treatment and follow-up periods, sending it within 5 days after being made aware of the pregnancy, to the CRO by e-mail or fax, to be forwarded to the Sponsor within 24 hours.

The Investigator is requested to follow each case of pregnancy exposure until the outcome.

If the pregnancy results in an abnormal outcome, this will be recorded in the eCRF as a SAE and managed as above described.

12. WITHDRAWAL CRITERIA

The patient may withdraw from the study at any time without explanation, without losing the right to future medical care. The participation of the patient may, at any moment, be terminated by the Investigator, if considered appropriate.

Study drug treatment must be terminated during the study for any of the following reasons:

- Any AE, including clinically significant abnormal laboratory value(s) which request treatment and study termination according to the Investigator's judgment.
- Patient who will discover an abnormal renal function (creatinine clearance ≤ 60 mLl/min) and/or an abnormal hepatic function (Child-Pugh class A to C) after laboratory blood and urine analysis data available.
- Patient who will become pregnant during the study.
- Request of the patient (without giving any reason).
- Investigator deems it to be in the best interest of the patient to discontinue.
- Failure to comply adequately with the dosing, evaluations, or other requirements of the study.
- If the patients meets an exclusion criteria (newly developed or not previously recognized) that precludes further study partecipation.
- Use of a prohibited CM.

- Patient does not achive adequate pain control by maximum allowed dose of rescue medication.
- Patient has overused rescue medication due to insufficient pain control.

The reason for the withdrawal must be well documented in the eCRF.

If a patient has been discontinued/withdrawn due to an SAE, the Investigator must immediately notify the relevant PhV contact (see Section 11.9). Any deviation from the protocol (to be classified as major or minor) will be accepted only in case of emergency and/or after a written agreement with the Sponsor.

Furthermore, any patient who prematurely terminates participation after having received any dose of the IMP will be encouraged to undergo an end of study examination according to the procedures and the time-window required for the End of study visit (Visit 2). If patient withdraws the consent, but is willing to have an End of Study visit, the End of study visit according to the described procedures (Visit 2) can be performed at that time.

If study participation is terminated due to an ADR, the patient has to be followed-up (with additional examinations, if necessary) according to the medical judgment of the Investigator, until the abnormal condition is resolved or the Investigator deems further observations or examinations as no longer medically indicated. Unless premature interruption occurs the End of study visit (Visit 2) will be the closure visit at clinical site.

13. LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

Before a patient is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the patient. These contact attempts should be documented in the patient's medical record or study file.

14. STATISTICS

The primary objective of the study is to evaluate the analgesic efficacy of DKP.TRIS/TRAM.HCl versus placebo 8 hours after the first dose, using a two-sided significance level of 5%. The secondary efficacy

objective is to evaluate the analgesic efficacy of DKP.TRIS/TRAM.HCl versus TRAM.HCl 8 hours after the first dose and after multiple doses, using a one-sided significance level of 2.5%.

The efficacy variables will be used to test both the superiority of DKP.TRIS/TRAM.HCl versus placebo (only for single-dose phase endpoints) and the non-inferiority with the possibility of switch to superiority of DKP.TRIS/TRAM.HCl versus TRAM.HCl. Data imputations will be considered for values collected after the RM intake and for intermediate missing data and missing data after early treatment discontinuation.
Details for the statistical analysis including the procedures for accounting for missing or spurious data and the patient analysis sets, will be specified in the statistical analysis plan (SAP). The SAP will be developed and finalized prior to database lock and the unblinding of the database.

14.1 Statistical Methods (Blinding and Randomization)

The study will be performed according to a randomized, double-blind, double-dummy, placebo and active-controlled, parallel group design, encompassing 2 study phases: a single dose-phase (first 8 hours) and a multiple-dose phase starting after single-dose phase.

Eligible patients, after successfully completing the screening phase for study eligibility assessment period on Day 1, will be randomized in a 4:4:1:1 ratio to 1 of the 4 possible treatment arms, as per treatment code delivered through IWRS in accordance with the randomization list, according to the following scheme:

Arm	Single-dose phase (t0-t8)	Multiple-dose phase (t8-day5)
1	DKP.TRIS/TRAM.HCl	DKP.TRIS/TRAM.HCl
2	TRAM.HCl	TRAM.HCl
3	Placebo	DKP.TRIS/TRAM.HCl
4	Placebo	TRAM.HCl

Double-blind conditions will be secured by using a double-dummy design.
DKP.TRIS 25 mg/TRAM.HCl 75 mg as well as the placebo tablets will be provided as film-coated tablets with matching appearance and weight.

The active comparator, TRAM.HCl 100 mg, will be provided as two capsules of a marketed drug Tramadol 50 mg and, for blinding, two capsules of placebo will be provided with matching appearance and weight.

The CRO or its delegate will be responsible for generating the randomization list that assigns the treatment to each patient. In order to preserve the double-blind conditions of the study, people who are involved in the preparation or the handling of the randomization list will not be involved in the study conduct and statistical analysis. This will remain in effect until the database is completed and locked.

A packaging randomization list will be prepared; one set will be provided for programming the IWRS and one set will be provided to the Clinical Trial Supply Department of A. Menarini Manufacturing Logistics and Services S.R,L., (MMLS), Via Sette Santi, 3 50131- Florence (Italy) for IMP/RM labelling operations.

All patients will be centrally assigned to randomized study treatment using an IWRS. Before the study is initiated, the log in information and directions for the IWRS will be provided to each study center. The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

14.2 Determination of Sample Size

A sample size of 510 patients is required to detect the difference between DKP.TRIS/TRAM.HCl and placebo and to demonstrate the non-inferiority of DKP.TRIS/TRAM.HCl versus TRAM.HCl for the time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours post-treatment.

In detail, a total number of 204 patients (102 for each treatment arm) was considered appropriate for detecting the superiority of DKP.TRIS/TRAM.HCl versus Placebo, assuming a power of 80%, alpha of 0.05, and a hazard ratio of 1.5 with a relative Wald confidence interval of 1.17 to 1.97 and the probability of event of 0.961 and 0.835 in the treatment and placebo groups, respectively (based on previous studies)..

Additionally, a total number of 408 patients (204 for each treatment arm) is sufficient for assessing the non-inferiority of DKP.TRIS/TRAM.HCl versus TRAM.HCl, assuming a hazard ratio of 1.06, a non-inferiority margin of 0.8, a power of 80%, alpha of 0.025, and proportions of events of 96.1% and 94.7%, respectively (based on previous studies).

In order to keep a 4:4:1:1 ratio the following number of patients by treatment arms will be recruited:

Arm	N
DKP.TRIS/TRAM.HCl+ DKP.TRIS/TRAM.HCl	204 patients
TRAM.HCl + TRAM.HCl	204 patients
Placebo + DKP.TRIS/TRAM.HCl	51 patients
Placebo + TRAM.HCl	51 patients

Assuming approximately 20% of screening failure rate, 612 patients are expected to be screened.

14.3 Analysis Populations

The following analysis populations will be considered for statistical analysis:

- Safety population: All patients randomized who have received at least 1 dose of the study treatment.
- Intention-to-treat (ITT) population: all patients randomized.
- Per-protocol (PP) populations: All patients of the ITT population who have not experienced major protocol violations that could affect the analyses. Different PP populations will be defined accordingly to the different analyses and the relative timepoint in the SAP. The PP populations will be used to perform the confirmatory analyses and to assess non-inferiority.

Efficacy analyses will be performed using the ITT population or PP population as defined in the SAP.

14.4 Analysis Variables

Efficacy Variables

Primary Efficacy Variables:

Time to first achieve an NRS-PI score <4 or a pain intensity reduction of ≥30% from drug intake till 8 hours after the first dose.

Secondary Efficacy Variables:

The following derivations apply:

- Total Pain Relief (TOTPAR):

TOTPAR is calculated as the time-weighted sum of the PAR-VRS scores.

The general formula for calculating $TOTPAR_x$ is as follows:

$TOTPAR_8 = \sum [T(i) - T(i-1)] \; x \; PAR(i)$ for i = 15m, 30m, 1h, 1.5h, 2h, 4h, 6h, 8h

$TOTPAR_{24} = \sum [T(i) - T(i-1)] \; x \; PAR(i)$ for i = from 10h to 32h

$TOTPAR_{48} = \sum [T(i) - T(i-1)] \; x \; PAR(i)$ for i = from 10h to 56h

$TOTPAR_{72} = \sum [T(i) - T(i-1)] \; x \; PAR(i)$ for i = from 10h to 80h

$TOTPAR_{96} = \sum [T(i) - T(i-1)] \; x \; PAR(i)$ for i = from 10h to 104h

$TOTPAR_{104} = \sum [T(i) - T(i-1)] \; x \; PAR(i)$ for i = 15m, 30m, 1h, 1.5h, 2h, 4h, 6h, 8h, 10h, …, 104h

where T(i) is the scheduled time, T(0) = 0, PAR(i) = PAR at time i.

Please note that starting from multiple phase values are collected before and two hours after each intake and that for the evaluation of $TOTPAR_{104}$ patients taking Placebo during the single phase will be excluded.

- Percent (%) max TOTPAR:

The max TOTPAR is calculated as the theoretical maximum time-weighted sum of the PAR values for each patient. The maximum possible TOTPAR is the value of TOTPAR that would be obtained if the patient has a complete pain relief for that observation period (ie, PAR at each post-baseline time point evaluated was 4).

The % max TOTPAR is the ratio between the TOTPAR of each patient and its theoretical maximum TOTPAR for a certain observation period.

- Summed Pain Intensity Difference (SPID):

SPID is calculated as the time-weighted sum of the pain intensity difference (PID) values, where PID is the difference in Pain Intensity calculated at each timepoint respect to the baseline value. The general formula for calculating $SPID_x$ is as follows:

$SPID_8 = \sum [T(i) - T(i-1)] \; x \; PID(i)$ for i = 15m, 30m, 1h, 1.5h, 2h, 4h, 6h, 8h

$SPID_{24} = \sum [T(i) - T(i-1)] \; x \; PID(i)$ for i = from 10h to 32h

$SPID_{48} = \sum [T(i) - T(i-1)] \; x \; PID(i)$ for i = from 10h to 56h

$SPID_{72} = \sum [T(i) - T(i-1)] \; x \; PID(i)$ for i = from 10h to 80h

$SPID_{96} = \sum [T(i) - T(i-1)] \; x \; PID(i)$ for i = from 10h to 104h

$SPID_{104} = \sum [T(i) - T(i-1)] \; x \; PID(i)$ for i = 15m, 30m, 1h, 1.5h, 2h, 4h, 6h, 8h, 10h, …, 104h

Please note that starting from multiple phase values are collected before and two hours after each intake and that for the evaluation of $SPID_{104}$ patients taking Placebo during the single phase will be excluded.

- Percent (%) max SPID:

The max SPID is calculated as the theoretical maximum time-weighted sum of the PID values for each patient. The maximum possible SPID is the value of SPID that would be obtained if the patient were pain free for that observation period (ie, PI at each post-baseline time point evaluated was 0).

The % max SPID is the ratio between the SPID of each patient and its theoretical maximum SPID for a certain observation period.

Single-dose phase:

- Pain Relief (PAR) scores at each prespecified time point (t15m, t30m, t1h, t1.5h, t2h, t4h, t6h, t8h) over the 8 hours after the first dose
- TOTPAR at 4, 6, and 8 hours (TOTPAR4, TOTPAR6, TOTPAR8) after the first dose
- Percentage of maximum TOTPAR (% max TOTPAR) at 4, 6, and 8 hours after the first dose
- Percentage of patients achieving at least 50% of maximum TOTPAR at 4, 6, and 8 hours after the first dose
- Pain Intensity (PI) scores at each prespecified time point (t15m, t30m, t1h, t1.5h, t2h, t4h, t6h, t8h) over the 8 hours after the first dose
- SPID at 4, 6, and 8 hours (SPID4, SPID6, SPID8) after the first dose
- Percentage of maximum SPID (% max SPID) at 4, 6, and 8 hours after the first dose

- Percentage of patients achieving at least 30% of PI reduction versus baseline at 4, 6, and 8 hours after the first dose
- PGE of the study medication at 8 hours after the first dose
- Time to RM: Time elapsed between treatment administration and the first dose of RM from baseline till 8 hours after the first dose
- Percentage of patients who required RM within the first 4, 6, or 8 hours post-dose.

Multiple-dose phase:

- Pain Relief (PAR) scores at each prespecified time point
- TOTPAR at 24, 48, 72, and 96 hours (TOTPAR24, TOTPAR48, TOTPAR72, TOTPAR96).
- Percentage of maximum TOTPAR (% max TOTPAR) at 24, 48, 72, and 96 hours of the multiple-dose phase.
- Percentage of patients achieving at least 50% of maximum TOTPAR at 24, 48, 72, and 96 hours of the multiple-dose phase.
- Pain Intensity (PI) scores at each prespecified time point over the multiple-dose phase.
- SPID at 24, 48, 72, and 96 hours (SPID24, SPID48, SPID72, SPID96) of the multiple-dose phase.
- Percentage of maximum SPID (% max SPID) at 24, 48, 72, and 96 hours of the multiple-dose phase.
- Percentage of patients achieving at least 30% of PI reduction versus baseline at 24, 48, 72, and 96 hours of the multiple-dose phase.
- PGE at 96 hours of the multiple-dose phase.
- Percentage of patients who required RM within 24, 48, 72, and 96 hours of the multiple-dose phase.
- Roland Morris Disability Questionnaire at 96 hours of the multiple-dose phase.
- Treatment Satisfaction Questionnaire for Medication at 96 hours of the multiple-dose phase

Complete treatment and assessment period (single and multiple-dose phase combined):

- Time to first achieve an NRS score <4 or a pain intensity reduction ≥30% from the first drug intake till 5 days post-treatment, excluding patients assigned to placebo treatment arm during the single dose phase.

- TOTPAR over 104 hours from the first drug intake till 5 days post-treatment (TOTPAR104), excluding patients assigned to placebo treatment arm during the single dose phase.
- SPID over 104 hours from the first drug intake till 5 days post-treatment (SPID104), excluding patients assigned to placebo treatment arm during the single dose phase.
- Time to RM: Time elapsed between the first drug intake till 5 days post-treatment, excluding patients assigned to placebo treatment arm during the single dose phase.

Exploratory variable:

Time to first achieve an NRS-PI score <4 **AND** a pain intensity reduction of ≥30% from drug intake till 8 hours posttreatment (single-dose phase only)

Safety Variables

The safety variables included:

- Adverse events (incidence, severity, seriousness, causality)
- Clinically significant changes in physical examination, vital signs, and laboratory test results post-dose versus baseline

For physical examination, laboratory tests, and vital signs, values collected during the Screening will be used as baseline values.

14.5 STATISTICAL ANALYSIS

.Descriptive statistics

All study variables will be presented by treatment and overall (if appropriate), by using the appropriate descriptive statistics according to the variable nature, unless otherwise specified:

- Continuous variables: number of non-missing observations, mean, standard deviation, minimum, median, maximum.
- Categorical variables: number of non-missing observations and column percentages (N, %).

Primary (efficacy) analysis

The primary efficacy variable, time to first achieve an NRS-PI score <4 or a pain intensity reduction ≥30% from drug intake till 8 hours after the first dose, will be analyzed for the superiority of DKP.TRIS/TRAM.HCl versus placebo on the ITT population using a Cox Proportional Hazard (CPH) model with treatment, baseline PI categories and baseline radiculopathy categories as covariates. A two-sided significance level of 5% will be used. In case of proportional hazard assumption is not satisfied additional analyses that permit relaxation of the assumption will be implemented.

Sensitivity analyses of the primary endpoint will also be done using the PP population.
Missing data and data collected after the RM intake will be handled as described in Section 0.

Sensitivity analysis

Sensitivity analyses will be conducted to the data imputation assumptions. Further details can be found in Section 0.

Secondary (efficacy) analysis

The secondary efficacy variable will be tested through an adhoc inferential analysis as below:

- Secondary efficacy variables with quantitative outcome:
  - PI-NRS, SPIDs, %max SPIDs, TOTPARs, %max TOTPARs, and TSQM will be analyzed by an analysis of covariance (ANCOVA) with treatment and the baseline PI-NRS as covariates;
  - Roland Morris Disability Questionnaire will be analyzed using ANCOVA, with treatment and the baseline Roland Morris Disability Questionnaire score as covariates. Additionally, percent improvement from Baseline in the Roland Morris Disability Questionnaire score will also be presented by treatment. Patients assigned to placebo treatment arm during the single dose phase will be excluded.
  - PGE (8h after the first dose, and at 96 hours of the multiple dose-phase) and PAR-VRS (at each time point separately) (ordinal variables) will be analyzed by Wilcoxon rank-sum test.
- Secondary efficacy variables with binary outcome will be tested using a Chi-squared test. An additional analysis considering adjustment by covariates (baseline PI categories and baseline radiculopathy categories) may be considered.
- Time to first use of RM will be assessed using a Log-rank test. An additional analysis considering adjustment by covariates (baseline PI categories and baseline radiculopathy categories) may be considered.
- The amount of RM consumption and the number of patients using RM will be descriptively analyzed

Non-inferiority of DKP.TRIS/TRAM.HCl versus TRAM.HCl will be tested with a one-sided significance level of 2.5%. Non-inferiority will be satisfied if the lower limit of the confidence interval is greater than a non-inferiority margin:

- For Time to "event" variables, the non-inferiority margin will be 0.80, based on Hazard Ratio.
- For continuous variables the non-inferiority margin will be 20%, based on the LS Mean.
- For binary variables the non-inferiority margin will be 0.80, based on the Odds Ratio.

In case the non-inferiority is confirmed, the superiority of DKP.TRIS/TRAM.HCl versus TRAM.HCl will be also tested. All the secondary endpoints related to the single phase will be also analyzed for the superiority of DKP.TRIS/TRAM.HCl versus placebo.

Non-inferiority will be tested on the PP population and in addition for the secondary endpoints of primary interest (TOPAR24, TOTPAR48) also on the ITT population. Superiority will only be tested on the ITT population, if non-inferiority is confirmed on the PP population.

Missing PI and PAR data and PI and PAR assessments collected after the RM intake will be handled as described in Section 0.

Exploratory (efficacy) analysis

Time to first achieve an NRS-PI score <4 **AND** a pain intensity reduction ≥30% from drug intake till 8 hours post-treatment (single dose phase only) will be analyzed analogously to the primary efficacy variable.

Subgroup analysis

There is no planned subgroup analysis; however, subgroup analysis may be conducted as post Hoc analysis.

Safety analysis

- Adverse events will be coded using the MedDRA dictionary (latest version available at the time of the analysis). The incidence of each treatment emergent AEs (TEAEs - AE's that occurred or worsened after the first administration of study treatment including the follow-up period [period between the last drug intake and the visit 2]) will be summarized by system organ class (SOC), preferred term (PT) and treatment.
- Reasons for early treatment termination will be summarized by treatment.
- Laboratory findings will be summarized as shift tables by treatment.
- Clinically significant abnormal findings in vital signs and physical examination will be listed by treatment.
- Safety analyses will be run on the safety population

Interim analysis and stopping rules

No interim analysis is planned for this study.

Data imputations

Data imputations will be done for PI and PAR assessments under the following circumstances:

- First, for values collected after the RM intake
- Then, missing data.

Once imputations are done, the efficacy variables based on PI and PAR assessments (SPID, TOTPAR, etc.) will be re-derived based on the PI and PAR imputed values.

Different strategies will be used to handle data imputation. A summary is provided in the table below:

	Values collected after the RM intake	Missing data
Main Analysis	**Single dose phase:** For all PI and PAR assessments at each timepoint after the first RM intake, PI will return to its baseline level and PAR to zero (Baseline Observation Carried Forward [BOCF]). **Multiple-dose phase:** PI and PAR assessments recorded during the 6 hours after the intake of RM (based on the effect of Paracetamol) will be replaced with the last observation carried forward (LOCF) (which should be the one done immediately before RM) or worst observation carried forward (WOCF) in case the assessment immediately before intake is missed.	Single missing values between measurements will be linearly interpolated; if more consecutive data are missed LOCF method will be applied
Sensitivity Analysis 1	**Treatment Policy Strategy:** values collected are used regardless of whether or not the RM is taken without any imputation.	No imputation, missing values will not be replaced.
Sensitivity Analysis 2	**Hypothetical Strategy:** a scenario is envisaged in which the intake of RM would not occur. Values collected for the 6 hours after the RM intake will be considered as missed and they will be imputed by using a multiple imputation approach.	If a Missing At Random (MAR) pattern of missing data is detected, missing values will be replaced by using a multiple imputation approach.

The SAP will provide additional details regarding methods for handling missing data and data collected after the RM intake for the main analysis and the sensitivity and exploratory analyses.

14.6 Protocol Deviations and Protocol Amendments

No deviations from the Protocol should be initiated without prior approval by the EC/HA of a protocol amendment according to applicable Regulations, except in case of emergency or when the change

involves only logistical or administrative aspects of the study. Any deviation from the Protocol, SOPs, GCP and applicable Regulatory Requirements should be immediately reported to the Sponsor.

Categories of protocol deviations will be defined before treatment unblinding and will be integrated in the statistical analysis. Details of major protocol violations, including those leading to exclusion from the PP population, will be documented in the SAP. For the final analysis, a blind data review meeting will take place at the end of the study in order to evaluate and accept the data management report, discuss remaining issues (outstanding queries, unresolved errors), and to confirm and approve relevant protocol deviations. After this final meeting has taken place and the database is considered cleaned, the database will be locked and unblinded.
Changes in the study protocol will require a protocol amendment. Such amendments will be agreed upon and approved in writing by all signatories of the protocol. If amendments are substantial, ie, are likely to have an impact on the safety of the patients, or to change the interpretation of the scientific documents in support of the conduct of the study, or if they are otherwise significant, the ECs and the CAs in the participating countries have to approve these amendments before implementation, according to applicable regulatory requirements

Changes which have no significant impact on medical or scientific validity of the study will be agreed upon and approved in writing by all signatories of the protocol and the EC will be notified of this protocol amendment. Any substantial amendments of the protocol will be integrated in an updated study protocol. The Principal Investigator must ensure full compliance with the updated study protocol.

14.7 Statistical Analysis Plan

The SAP will be finalized before the unblinding of the study. The SAP will describe in detail study endpoints and statistical analyses, including the analysis of the primary as well as additional endpoints. In case changes of the original primary endpoint or of the original primary analyses will occur during the study, these changes will be the patient of a substantial protocol amendment.
All statistical analyses not prespecified and run after data unblinding will be considered additional/exploratory analyses.

15. STUDY DISCONTINUATION AND CLOSURE

In case the study is temporarily suspended or prematurely terminated, written notification documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study patients, Investigators, ECs, Sponsor and Regulatory Authorities with the reason(s) for the termination or suspension. The study patients will be contacted, as applicable, and be informed of changes to study visit schedule.

16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator must permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents. The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Source documents are filed at the Investigator's study center.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

17. QUALITY CONTROL AND QUALITY ASSURANCE

17.1 Study Monitoring/Data Quality Control

Site monitoring is conducted to ensure that the rights and well-being of study patients are protected, that the reported study data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol/amendment(s), with International Council for Harmonisation-Good Clinical Practice (ICH-GCP), and with applicable regulatory requirement(s).

The Investigator will be contacted by the study monitor on a regular basis. The monitor will have the responsibility of reviewing the ongoing study with the Investigator to verify adherence to the protocol and to deal with any problems.

The Investigator agrees to allow access to all study materials needed for the proper review of study conduct. The Investigator agrees to assist the monitor in resolving any problem that may be detected during the monitoring visit or data cleaning process.

17.2 Case Report Forms

Data collected during the study will be recorded in the eCRF. Data reported on the eCRF must be consistent with the source documents. The Investigator must ensure the accuracy, the completeness and the consistency of the data entered in the eCRF.

On the eCRF, patients will be identified by the patient number/code, assigned at the Screening Visit. The patient number/code will be a number composed of numeric values.

During the conduct of the clinical part of the study, the eCRF must be available and up-to-date, so that it always reflects the latest observations on the respective patient.

The Investigator or designee will be responsible for entering study data into the eCRF in accordance to the eCRF user guidelines.

17.3 Quality Assurance

All clinical activities conducted under this protocol are subject to GCP regulations. This includes audits/inspections by the Sponsor, and/or by national/international HA representatives at any time. Principal Investigators must agree to the inspection of the study site, facilities, and of study related records by the HA representatives and/or by the Sponsor, and/or its delegates, which must be performed in accordance with national laws concerning personal data protection.

18. ETHICS ASPECTS

The study will be carried out in compliance with the study protocol, the recommendations on biomedical research on human patients of the Declaration of Helsinki, ICH-GCP Guidelines, EU-Directives and Regulations (where applicable) and national requirements of the participating countries.

18.1 Ethics Committees

Before starting the study in a study site, Study Protocol and relevant documentation (Patient information leaflet, Informed Consent Form and the Investigator's Brochure and other documents, according to National Regulations) must be submitted to and approved by the EC and the HAs of the participating countries.

In addition, all local national legal requirements for the conduct of a clinical study have to be followed. Any amendment to the protocol will be submitted to the ECs and HAs before implementation.

Furthermore, the HAs and ECs of the participating countries will be informed about the study start, the end of the study, or the premature study termination as appropriate and within the requested time period.

18.2 Subject's Insurance

For patients participating in the study, Sponsor will issue an insurance policy in accordance with local regulatory requirements.

Details on the insurance company, the insurance number and conditions will be made available to patients in the ICF and/or provided as a separate document, in accordance with national requirements. Insurance policy will be submitted for approval to the ECs along with the other study documents.

A copy of the insurance certificate will be provided to each Investigator and will be filed in the Investigator's File at the sites and in the study's Trial Master File (TMF).

The Investigator must notify to Sponsor immediately upon notice of any claims or lawsuits.

19. DATA PROTECTION LAWS COMPLIANCE

All clinical study information shall be recorded, processed, handled, and stored in such a way that it can be accurately reported, interpreted and verified; at the same time, the confidentiality of records and of the personal data of the patients shall remain protected in accordance with the applicable law on personal data protection such as the EU General Data Protection Regulation 679/2016 and the EU Regulation on clinical trials on medicinal products for human use 536/2014.

This section defines the appropriate technical and organizational measures that shall be implemented to protect information and personal data processed against unauthorized or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss as well as to assure the fulfilment of patients' privacy rights.

19.1 Acknowledgment

The Site, the Principal Investigator, the Centralized Laboratory, the CRO as well as their appointed staff and service providers acknowledge that: (a) the performance of the study will imply processing

of sensitive personal data; (b) personal data processing is regulated by the applicable European (ie, the EU General Data Protection Regulation 679/2016 and the EU Regulation on clinical trials on medicinal products for human use 536/2014) and local laws (ie, the laws of the country where the study is conducted) as well as by the Sponsor's national legislation.

In particular, it is hereby acknowledged that being the Sponsor a company incorporated under Italian law, it has to mandatorily comply with Italian legal provisions on data protection: therefore, the Site, the Principal Investigator, the Centralized Laboratory, the CRO shall cooperate with the Sponsor to allow the fulfilment of such obligations; (c) strict compliance with the applicable data protection laws and this section of the protocol is deemed by the Sponsor as an essential condition of collaboration with the Site, the Principal Investigator, the Centralized Laboratory, the CRO.

19.2 Data Controllers and Data Processors

The Sponsor, the Site, the Principal Investigator and the CRO acknowledge that according to the applicable privacy laws, Sponsor and Site will act as independent data controllers while CRO and the Principal Investigator will act as data processors respectively of the Sponsor and of Site. Before the beginning of the study, the Site will instruct in writing Principal Investigator as its data processor[4]. However, if specific local laws or regulations mandate a different definition of the privacy roles, the Sponsor, the Site, the Principal Investigator and the CRO will implement the relevant legal instruments (eg, if pursuant to the local laws the Site is a data processor of the Sponsor, a Data Processing Agreement will be finalized; if pursuant to the local laws Sponsor and Site are joined controllers, a Joint Controllership Agreement will be finalized).

[1] For clinical trials where the Principal Investigators are the owners of the Site, this provision may not apply. In such cases, the Principal Investigator might be considered as a Data Controller

19.3 Duties of the Parties involved in the performance of the study

Collection and use of patients' data, including their biological samples, will be carried out in full respect of the provisions of the information notices submitted to patients, as well as the privacy rights, the fundamental freedoms, and the dignity of data patients. All the parties involved in this study undertake to adopt adequate measures to warrant that data will always be processed securely and in compliance with privacy laws. The Site, the Principal Investigator, the Sponsor, the CRO and the Centralized Laboratory as well as their appointed staff and service providers, each in its respective remit and within the limits of their specific role in the study, shall implement the

following safety measures (physical, logical, organizational, technical, electronic, I.T. etc) to ensure adequate protection of the personal data of the patients involved in the study. In particular:

(i) DATA SAFETY. The Site and/or the Principal Investigator shall adopt all the necessary measures to prevent or minimize the risks of theft, fire, flooding, partial or total loss, accidental disclosure or illegal/unauthorized access to patient's data or Sponsor's proprietary confidential information; to this extent, before the beginning of the study, the Site and/or the Principal Investigator shall ensure that the actual measures they have implemented are fit-for purpose and law-compliant, and in particular:

- in order to minimize the risk of unauthorized access and theft, the hardware on which patients' personal data are stored shall be placed in a restricted-access area, accessible only to those individuals who need to retrieve the patients' personal data included in the database for professional purposes; the same safeguards shall be put in place for non-electronic databases;
- any electronic database containing the patients' personal data shall be password-protected by means of a strong password. Systems shall be set so that passwords must be updated at least every three months and feature at least 8 characters, with upper-case and lower-case recognition, containing at least three "special" characters, such as upper-case letters [A-Z], lower case letters [a-z], numbers [0-9], symbols [!, #, $, etc] or other special characters [Á, ë, ö etc]. Passwords shall not include elements which may easily be associated with the assignee or information regarding him/her, such as name and year of birth (eg, "johnbrown80") or easily predictable strings of characters (eg, "qwerty", "12345", "admin", "user", etc.);
- adequate cryptographic protection measures shall be put in place for data "at rest" and "in transit" (these include, for example, file system or database cryptography, or any other equivalent IT measure which renders data unintelligible to those who are not authorized to access them);
-high level security measures shall be implemented also on the files or databases which contain the "key" to match the patients' personal data (ie, name, surname, etc) with their respective "Patient IDs" (as defined at point *(iv)* below);
- Backup processes and other measures that ensure rapid restoration of business-critical systems shall be implemented;
- Updated Antivirus and firewall programs shall be installed on the IT devices.

- The patient diary must be handed in, in person by the patient. If this is not possible, it must be secured. A secure courier service should be used to collect the diary.
The Site shall, regularly test and update the measures listed above. The Site shall, upon request from the Sponsor and/or the CRO, provide detailed written information about the measures listed above. The CRO shall ensure that the selected sites for the study have implemented the above listed measures.

(ii) TRANSMISSION OF DATA. All the parties that transfer data through internet and/or to the centralized database(s) used to process study's data or to generate statistical analyses shall implement secure protocols based on cryptographic standards which make data unintelligible to unauthorized individuals.

(iii) SECURITY OF THE CENTRALIZED DATA BASE. The centralized database held by the Sponsor shall have the following safeguards in place: - appropriate authentication methods, which differentiate between different users according to their respective roles so as to ensure that access to a specific set of patients' data is permitted exclusively to those for whom access to such data is essential in the context of their work for the study; - appropriate measures to ensure that the authentication credentials are periodically updated (ie, password change);
(iv) PSEUDONYMIZATION. All personal data that may allow identification of the patients involved in the study shall be adequately dissociated from the other data pertaining to the study ("pseudo-anonymisation" process). The Principal Investigator shall adequately dissociate the identification data of patients from the data pertaining to the study by linking results to an alphanumerical code ["Patient ID"], whose format shall not make it possible to identify the patient directly or indirectly, so as to ensure that only anonymous data are transmitted to the Sponsor, the Centralized Laboratory and /or the CRO. Site/Principal Investigator shall securely store a separate list (eg, identification log) with the identification code, together with all signed informed consents, in accordance with the security measures as defined above.
The patient code pairing list (ie, the list that where the Patient ID is linked to the patients' identification data such as name and surname), shall be archived by the Principal Investigator.

As outlined below, samples shall only be stored for as long as strictly necessary for the study's performance and should be destroyed after the analysis. Biological samples and any other examination (eg, X-ray, ECG) shall bear Patient ID, and in no case will they bear other information that may lead to the direct or indirect identification of the patient, especially when, in accordance with this protocol, samples shall be forwarded and shared outside the clinical Site (eg, in case of centralized reading or local laboratory analysis).

(v) TRAINING. The parties shall ensure that any personnel involved in the study have received proper training on data protection issues. All actions related to the implementation of the afore mentioned measures shall be provided by the Sponsor, the Center and/or the CRO to the competent authorities (including data protection authorities) and EC if and when requested. If such authorities or the Sponsor consider the implementation of the afore mentioned measures insufficient to guarantee an adequate level of protection of the patients' personal data, The Site, the Principal Investigator, the CRO and the Centralized Laboratory undertake to adopt all the necessary activities to overcome such remarks to assure the full compliance with the data protection laws.

19.4 Data Breach

Data Breach is an incident regarding personal data security and leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored or otherwise processed. In particular: destruction of personal data is where the data no longer exists, or no longer exists in a form that is of any use to the Site, sponsor, CRO, Principal Investigator etc. data loss is when the data may still exist, but the Site, sponsor, CRO, Principal Investigator etc. has lost control or access to it, or no longer has it in its possession; damage is where personal data has been altered, corrupted, or is no longer complete; data unavailability is where, following a data incident (such as a network outage, a natural or manmade disaster, etc), personal data become temporarily inaccessible to the Site, sponsor, CRO, Principal Investigator etc. Anomalous Event is an event that is not part of the standard operational scope of an infrastructure, network or service and which affects, or is likely to affect, personal data; this may include theft or loss of IT devices and other physical events (eg, an unauthorized access to a locked storage room containing paper files with personal data), and/or electronic/IT anomalies (eg, cyber-attacks, default or hacking of cloud services), which may in any way entail loss, unavailability,

alteration, theft, copy or dissemination of personal data. Whoever becomes aware in any way of an Anomalous Event and/or of a Data Breach (see definitions above) affecting the patients' personal data and/or personal data collected in the context of the study shall, as appropriate, immediately (and in any case no later than 24 hours from the knowledge of an Anomalous Event and/or of a Data Breach) inform the Clinical Operations Director, the sponsor's Data Protection Officer, the Site and the CRO (CRO responsible persons for data breach incidents management – Kim Gray [PrivacyOfficer@IQVIA.com]) and shall provide the following information:

(i) Anomalous Event / Data Breach Type (eg, data loss, unauthorized access, loss of company device, etc.);

(ii) Person or source that first reported the Anomalous Event/ Data Breach;

(iii) Date and Time when the person who first reported the Anomalous Event / Data Breach became aware of it;

(iv) Anomalous Event / Data Breach Date and Time (actual or presumed);

(iv) Place (specify if actual or alleged) where the Anomalous Event / Data Breach occurred;

(v) Anomalous Event / Data Breach Description;

(vi) Indicate the source of the Anomalous Event / Data Breach (eg, I.P. source) - (if relevant);

(viii) Indicate the affected infrastructure / system / application / cloud/ software / hardware database and their location;

(ix) List or describe the processing/storage systems affected by the Anomalous Event/Data Breach (if relevant);

(x) Number of data patients involved (if known);

(xi) Amount of allegedly breached data

(xii) Other relevant information.

Once all the above information has been provided, the Sponsor and/or the Site should have a reasonable degree of certainty that a security incident has occurred that has led to personal data being compromised.

Then, as appropriate, Sponsor and Site, each one in its respective remit, shall manage the Data Breach in accordance with the applicable data protection regulations.

For Data Breach affecting personal data of patients enrolled within the European Union, Sponsor and Site autonomously or jointly depending on the circumstances and their privacy responsibilities as defined by the Regulation 679/2016- shall:

1. Collect the necessary evidence and information;
2. Categorize the breach;
3. Determine the risk probability and level to the rights and freedom of the concerned patients;
4. Identify and put in place appropriate remedies to minimize the impact of the Data Breach;
5. Determine the notification and communication duties vis à vis the competent supervisory authority and/or the concerned patients.

19.5 Information Notice on Personal Data Protection and Pseudo-anonymization

Prior to patients' enrolment in the study, the Principal Investigator and/or the Site (including their personnel) shall provide each patient with adequate, law-compliant "information notices and consent forms to process personal data" as included in the ICF (or, as the case may be, through a separate, specific form) provided by the Sponsor or delegated CRO and shall collect his/her written consent to the processing of personal data according to the actual performance conditions in which the study is carried out. The Principal Investigator is responsible to archive the signed ICF in accordance with the security measures described above. Among other things, the ICF (or the separate form) shall inform patients about:

(i) the applicable data protection legislation

(ii) what kind of data shall be collected during the study listing them in detail or by category;

(iii) the purpose of data processing (eg, performance of the study, pharmacovigilance) and the legal basis;

(iv) whether granting the consent(s) to process personal data is a necessary or an optional condition to take part in the study;

(v) the use of data for future scientific researches / secondary use of data (if any). In such a case the future scientific purposes / secondary use shall include the future / further scientific processing activities/purposes;

(vi) the pseudonymization procedure and scope;

(vii) who can access patients' data and under what circumstances;

(viii) the period of data retention/storage as defined in *Paragraph 19*, including the storage of the biological sample;

(ix) to which entities/countries outside the EU patients' data will be transmitted (if applicable), as per *Paragraph 18.7.*

(x) patients' data protection rights as defined by the EU General Data Protection Regulation 679/2016.

(xi) Data Controllers / Data Processors and the relevant contact details

(xii) Sponsor's Data Protection Officer contacts (DPO)

(xiii) in case of genetic data processing the possible findings, also with regard to unexpected findings that might be disclosed on account of the processing of the genetic data.

19.6 Genetic Data

Genetic data will not be collected for this study.

19.7 Transfer of subjects' data outside the European Union

The study performance entails transferring patients 'personal data (coded data) outside the EU. To this extent, the Sponsor, the Site, the Principal Investigator, the Centralized Laboratory, the CRO, undertake to export such data in compliance with adequate safeguards/legal basis as required by the Regulation 679/2016 including the Commission Decisions, the Standard Contract Clauses, the Privacy Shield, patients' specific consent.

19.8 Exercise of subjects' data privacy rights

Each study patient has the right to contact the Sponsor, the Site, the Principal Investigator, the Centralized Laboratory, the CRO to exercise the rights afforded to the patient by the law, including the afforded ones under articles 15 to 22 of Regulation (EU) 2016/679, namely: knowing whether or not any data referring to his/her is being processed in the context of the study; access his/her data; verify the data's content, origin, exactness, location (including, where applicable, the non-EU countries where the data might be); obtain a copy of the data including their transmission to another entity indicated by the patient; ask that the data are supplemented, updated, amended; in the circumstances set forth by the law, ask that the processing of data is restricted, that data are anonymized or frozen; oppose to the processing of his/her data for legitimate reasons. Each patient has the right to lodge a complaint with his/her local supervisory authority and/or to notify to the Data Protection Officer any use of his/her personal data the patient regards as inappropriate. Each study patient is free to withdraw at any time from the study. In such case, each study patient may ask the

Sponsor, the Site, the Principal Investigator, the Centralized Laboratory, the CRO to destroy/delete his/her personal data (IF APPLICABLE: including his/her biological samples, unless they have been permanently anonymized), thus preventing any further processing or analysis of his/her data. However, data and results of tests that may have been used to determine the results of the study shall not be deleted, to avoid altering or impairing altogether the results of the study. Specific rights in relation to the processing of genetic data applies. Please Refer To Paragraph 18.6. If the Site, the Principal Investigator, the Centralized Laboratory, the CRO receive a request for data privacy rights exercise, the concerned recipient shall immediately inform the Sponsor DPO by e-mail at dpo@menarini.com. The request shall be fulfilled within the term set forth by the applicable privacy laws (normally 30 days). The Sponsor, the Site, the Principal Investigator, the Centralized Laboratory, the CRO shall implement adequate organizational measures to reply to patients within the above-mentioned deadline.

19.9 Future research

With patients' optional and additional consent, the Sponsor and/or the Center may use the data collected during the course of the study for further medical and scientific research purposes. These may include, for example: retrospective clinical studies; clinical studies pertaining to the patients' pathology/medical condition(s)or similar conditions; studies which compare the data of this Study with those from other sources to identify the factors involved in a disease; registration of new drugs.

In the context of these additional research activities, patients' data will be processed, pseudonymized and transferred abroad and may be shared with future research partners. In the context of these additional research activities, patients' data will be processed, anonymized and transferred abroad, and may be shared with future research partners - in most cases this will prevent patient's identification; however, in the unlikely event patient's full identity really needs to be disclosed, the same precautions and safeguards as those described in this protocol will be implemented.

20. DATA HANDLING AND RECORDS KEEPING

Unless other laws require archiving for a longer period, the Center and the Principal Investigator shall archive the content of the clinical study file, including the relevant patients' personal data, for

at least 25 years after the end of the clinical study. However, medical records shall be archived in accordance with the national laws of the country where the study is performed.

The Investigator should keep all study-related documents, as specified in ICH E6 (GCP) Section 8 and by the applicable regulatory requirement(s), in the Investigator's File. The media used to archive the content of the clinical study file shall be such that the content remains complete and legible throughout the period referred to in the first paragraph. Any modification to the content of the clinical trial master file shall be traceable.

The content of the Investigator's File shall be archived in a way that ensures that it is readily available and accessible, upon request, to the competent authorities. If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility.
The Sponsor must be notified in writing of the name and address of the new custodian.

21. PUBLICATION POLICY AND RESULTS

By signing the study protocol, the Investigator (and his/her appointed staff) ensures that any information and all the study documents provided by the Sponsor will be maintained strictly confidential. None of this material may be disclosed to any party not directly involved in the study without written permission from Sponsor. All information concerning the study, the drug as well as data and results of the study are confidential and property of the Sponsor.

The Sponsor will prepare the final report, including the statistical and clinical evaluations, and study results will be posted and made public, according to applicable Regulatory Regulations. The Investigator's agreement and signature will be obtained, and a copy will be provided to the Investigator. Sponsor reserves the exclusive right to publish and present data and results of the present study at scientific meetings, or to submit these clinical study data to national and international Regulatory Authorities. The Investigator may not use the results of this study for publication or presentation without written authorization from Sponsor.

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23. Protocol Approval Page

Study Title: A randomized, double-blind, placebo-controlled, parallel arm group study to evaluate the analgesic efficacy and safety of Dexketoprofen trometAmol aNd tramadol hydrochloride oral fixEd dose combination on moderate to severe acute pain in patients with acute low back pain - DANTE study

Code: MEIN/18/DEX-LBP/001

EUDRA-CT number: 2019-003656-37

The signers confirm that they have read and approved the protocol

Study Medical Expert: Deniz Coskunsever

Signature & Date: _____ 29 / 09 /2021

Corporate Medical Director: Lorenzo Melani

Signature & Date: _____ 29 / 09 /2021

Coordinating Investigator: Prof. Giustino Varrassi

Signature & Date: Giustino Varrassi 29 / 09 / 2021

Statistician Giorgio Reggiardo

Signature& Date: _____ 29 / 09 / 2021

24. Investigator's approval Page

INVESTIGATOR'S APPROVAL PAGE
(original to be kept in the Trial Center File)

I understand that all information concerning the product Menarini Pharmaceutical supplied in connection with this study protocol are confidential information. This information includes: Protocol, Investigator's Brochure, Case Report Form, Other documents _____.

I understand that any change in this study protocol must be approved in writing by Menarini Pharmaceutical and the Co-ordinating Investigator, submitted to the Ethics Committee and Health Authorities before implementation, except where necessary to eliminate apparent immediate hazard to patients.

I confirm that I will conduct the study according to this protocol, the Good Clinical Practice (GCP), the Declaration of Helsinki and laws and regulations in the Country where the study is to be conducted.

I confirm that I will record and report all adverse events occurring during the study, according to this protocol.

I confirm that I am informed about the need of data records retention, according to current regulations and that no data can be destroyed without the written consent of Menarini Pharmaceutical.

I confirm that I will transfer adequate ownership of my responsibilities for the trial and will inform the Sponsor in case I retire from my PI role.

I confirm that in case the Trial Center File is stolen or anyhow damaged, I will promptly inform the Sponsor and declare it to the Competent Authorities.

Principal Investigator: _____

Signature & Date: _____

25. APPENDICES

25.1 Appendix 1: Declaration of Helsinki