MENARINI RICERCHE

DAVID

Dexketoprofen **A**nalgesic e**V**olution w**I**th trama**D**ol- **DAVID Study**

CLINICAL TRIAL PROTOCOL

FINAL VERSION 2.0*, 24 NOV 2015

Analgesic efficacy of oral dexketoprofen trometamol/tramadol hydrochloride versus tramadol hydrochloride/paracetamol: a randomised, double-blind, placebo and active-controlled, parallel group study in moderate to severe acute pain after removal of impacted lower third molar.

Study code	DEX-TRA-06
EudraCT-Number	2015-004152-22
Investigational Medicinal Product	Dexketoprofen trometamol 25mg /Tramadol hydrochloride 75mg
Development phase of study	III b
Sponsor	**MENARINI RICERCHE SpA** Via Sette Santi 1, 50131 Firenze (Italy)
Co-ordinating Investigator	[redacted]

STATEMENT OF CONFIDENTIALITY

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*version 2.0 represents an editorial upgrade of version 1.0 which has never been submitted to any Competent Authority

1. SIGNATURES

The signatories have read the clinical trial protocol titled *"Analgesic efficacy of oral dexketoprofen trometamol/tramadol hydrochloride versus tramadol hydrochloride/paracetamol: a randomised, double-blind, placebo and active-controlled, parallel group study in moderate to severe acute pain after removal of impacted lower third molar. (**D**exketoprofen **A**nalgesic e**V**olution w**I**th trama**D**ol - **DAVID Study**)"* - ***Final Version 2.0, 24 NOV 2015*** - carefully and agree to adhere to its provisions. Changes to the protocol have to be stated by the sponsor in amendments to the clinical trial protocol which, if they are substantial, have to be authorised by the Competent Authorities and Ethics Committees before translating them into action.

Sponsor's Representative	**Signature**	**Date**
[redacted]	.....	.....

Co-ordinating Investigator	**Signature**	**Date**
[redacted]	.....	.....

1.1 Principal Investigator's Statement

My signature below documents my agreement with the contents of this clinical trial protocol titled *"Analgesic efficacy of oral dexketoprofen trometamol/tramadol hydrochloride versus tramadol hydrochloride/paracetamol: a randomised, double-blind, placebo and active-controlled, parallel group study in moderate to severe acute pain after removal of impacted lower third molar. (**D**exketoprofen **A**nalgesic e**V**olution w**I**th trama**D**ol - **DAVID Study)" - **Final Version 2.0, 24 NOV 2015* -** with regard to the execution of the study and the required documentation/data collection. I agree to comply with this clinical trial protocol in its entirety and with the ICH guidelines for Good Clinical Practice (GCP).

Principal Investigator	**Signature**	**Date**
.....	.....	.....
(printed name)		

2. PROTOCOL SYNOPSIS

Study Title, Study Code and Nick name /Acronym	Analgesic efficacy of oral dexketoprofen trometamol/tramadol hydrochloride versus tramadol hydrochloride/paracetamol: a randomised, double-blind, placebo and active-controlled, parallel group study in moderate to severe acute pain after removal of impacted lower third molar. (**D**exketoprofen **A**nalgesic e**V**olution w**I**th trama**D**ol - **DAVID Study**) Study code: DEX-TRA-06
Phase	Phase IIIb
Indication	Moderate to severe acute pain following impacted lower third molar extraction.
No. of sites &countries	Approximately 20 sites among Europe and Turkey.
Investigational Medicinal Product (IMP)	Dexketoprofen trometamol 25mg /Tramadol hydrochloride 75mg film-coated tablet (DKP.TRIS/TRAM.HCl 25mg/75mg).
Reference therapy	– Tramadol hydrochloride 75mg/paracetamol 650mg film-coated tablet, as 2 x [37.5mg/325mg] (TRAM.HCl/paracetamol 75 mg/650 mg) – Matching placebo
Treatment regimen	All study treatments will be administered as single oral dose; double dummy technique will be applied to ensure double-blind condition.
Rescue medication (RM)	Ibuprofen 400mg tablets.
Design	Multicentre, randomised, double-blind, double-dummy, parallel-group, placebo and active-controlled, single-dose study. Eligible patients will be randomised in a 2:2:1 ratio to one of the 3 possible treatment arms: – DKP.TRIS/TRAM.HCl – TRAM.HCl/paracetamol – Placebo
Primary objective	To assess the comparability of DKP.TRIS/TRAM.HCl and TRAM.HCl/paracetamol in terms of analgesic efficacy on moderate to severe pain following impacted lower third molar extraction.
Secondary objectives	To confirm the safety and tolerability profile of DKP.TRIS/TRAM.HCl following single dose administration.
Study duration	The individual study participation will last approximately 3 weeks, including: – Screening period, for study eligibility assessment (within 2 weeks prior to randomisation), which includes the prior to surgery, surgery, and qualification steps.

	– Randomisation, treatment administration and efficacy assessment period (day 1). – End of study visit (6±1 days after randomisation). The overall clinical phase is planned to start in 1H 2016 and to be completed within the Q4 2016. The enrolment will be competitive.
Inclusion criteria	To be eligible for this study, EACH of the following criteria must be satisfied: 1. Properly executed written informed consent. 2. Male or female patients aged more than 18 years. 3. Scheduled for outpatient surgical extraction -under local anaesthesia (i.e. 2% lidocaine with 1:80,000 epinephrine) - of lower third molar teeth, with at least one of which fully or partially impacted in the mandible requiring bone manipulation (e.g. level B or C plus class II or III of the Pell-Gregory scale). 4. Females participating in the study must be either: – Females of non-childbearing potential, defined as any woman who had undergone surgical sterilization or is more than 2 years post-menopausal; – Females of childbearing potential provided that they have a negative pregnancy test at baseline (screening and qualification period) and are routinely using an effective method of birth control resulting in a low failure rate (i.e. hormonal contraception, intrauterine device, condoms in combination with a spermicidal cream, male partner sterilization –vasectomy– or total sexual abstinence). 5. Mentally competent, able to understand and give written informed consent prior to study entry. 6. Compliant to undergo all visits and procedures scheduled in the study, including recording of pain assessments on the electronic diary (e-Diary) as required by protocol. After surgery, patients will be eligible to progress with randomisation ONLY if the following criterion is also met: 7. Pain of at least moderate intensity in the first 4 hours after the end of surgery (NRS score $\geq$ 4).
Exclusion criteria	To be eligible for this study, NONE of the following criteria must be satisfied: 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, concomitant medication (CM) and concurrent systemic diseases. 2. Clinically significant abnormalities in the vital signs (VS) and / or safety laboratory tests, as per investigator's judgement.

	3. History of allergy or hypersensitivity to the study treatments, RM or to any other NSAIDs, opioids and acetyl salicylic acid. 4. History of peptic ulcer, gastrointestinal disorders by NSAIDs or gastrointestinal bleeding or other active bleedings. 5. History of severe asthma. 6. Moderate to severe renal dysfunction, severe hepatic dysfunction or severe cardiac dysfunction. 7. Coagulation disorders. 8. History of, or current epilepsy. 9. Patients with Crohn's disease or ulcerative colitis. 10. Patients using and not suitable for withdrawing analgesics within 12 hours before surgery (5 days prior to the surgery day in case of COX-2 inhibitors) and for 8 hours post-dose [analgesics other than those specified in the protocol (namely study treatments and RM)]. 11. Patients using and not suitable for withdrawing alcohol, sedatives (e.g. benzodiazepines) and hypnotic agents within 12 hours before surgery and for 8 hours post-dose. 12. Chronic opioid treatment (major opioids and tramadol). 13. Patients using and not suitable for withdrawing the following prohibited medications, within 48 hours or 5 half-lives (whichever the longer) prior to the start of surgery and for 24 hours post-dose: – Anticoagulants, thrombolytic and antiplatelet agents – Corticosteroids (with the exception of inhalers or topical agents); – Monoamine oxidase (MAO) inhibitors (a minimum of 14 days must elapse prior to the start of surgery); – Antiepileptics; – Antipsychotics; – Serotonin reuptake inhibitors and tricyclic antidepressants; – Lithium; – Methotrexate; – Antibacterial sulfonamides. 14. Participation in other clinical studies in the previous 4 weeks. 15. 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). 16. 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. 17. Pregnant and breastfeeding women. NOTE: a pregnancy test will be performed to all women of childbearing potential at Screening and another one on the day of surgery prior to randomisation.

	After surgery, <u>patients will not be eligible to progress with randomisation if the following criterion is also met:</u> 18. Surgical complication that, in the opinion of the Investigator, advises against their inclusion in the study.
Study procedures and Efficacy and Safety assessments	Prior to any study-related procedure, the patient's written informed consent form (ICF) must be obtained. **<u>Screening period (within 2 weeks prior to randomisation)</u>** ▪ ***Prior to surgery*** The following procedures/assessments must be completed during the screening period and prior to the surgery day (day 1): – Collection of demographic data. – Recording of medical history. – Recording of prior and concomitant medications (CMs). – Physical examination including body weight (BW), height (H), and vital signs (VS) (blood pressure [BP], heart rate [HR]). – Laboratory safety tests (haematology, clinical chemistry, coagulation test and urinalysis). – Pregnancy test (if applicable). – Instructions regarding how to complete patient's pain and analgesia assessments, RM intake and [redacted] functionality on e-Diary. – Recording of adverse events (AEs) occurred since the ICF signature, if any. – Check of inclusion and exclusion criteria. ▪ ***Surgery*** The surgical procedure will be performed under local anaesthetic block using 2% lidocaine with 1:80,000 epinephrine up to a total volume of 5.4 mL per molar. Surgery shall be performed at least one day apart pre-surgery procedures have been completed. ▪ ***Qualification*** After completion of surgery (last suture), patients will be followed for a period of up to 4 hours and the following will be performed/assessed: – Instruct patients to inform the investigator when they experience pain. – Dispensing of the e-Diary and testing its main functions. – VS measurement. – Pregnancy test (if applicable). – Recording of AEs and changes in CM, if any, since the last assessment. – Review/Check of inclusion/exclusion criteria. Patients reporting pain within 4 hours after the end of surgery will be asked to rate their pain intensity (PI) on the e-Diary to assess their

eligibility for randomisation. Patients must describe their PI in response to the question: *'How do you rate the intensity of your pain?'* using an 11-point Numerical Rating Scale (NRS) ranging from 0 (no pain) to 10 (worst pain).

NOTES:
1. Only patients experiencing pain of moderate or higher intensity (NRS score ≥4) within the first 4 hours after the end of surgery will be eligible for randomisation.
2. A patient can be screened a maximum of 2 times, provided that he/she was not already randomised and all the inclusion and none of the exclusion criteria are met.
3. Pregnancy test should not be repeated during the qualification period if it was performed the day before as screening procedure.

Randomisation, treatment administration and efficacy assessment period (day 1, t_0 - t_{8h})

- ***Randomisation and treatment administration (t_0)***

Patients successfully completing the qualification period will be randomised through IxRS to one of the three possible treatment arms (DKP.TRIS/TRAM.HCl, TRAM.HCl/paracetamol or placebo) and the corresponding study treatment will be given, as one single oral dose. NRS-PI **immediately prior** to the administration of the study treatment will be recorded as baseline PI (t_{0h}).

A box of RM (ibuprofen 400mg tablets) will be assigned by IxRS and provided to the patients that will be instructed about its usage. A paper diary for RM recording intake will be also given to patients, with the request to return it to the site at the End of Study visit.

- ***8-hour pain and analgesic effect assessment period ($t_0 - t_{8h}$)***

After the study treatment administration, patients will remain under observation at site for two hours (up to t_{2h}).
Pain and analgesia assessment by patients will be performed either at site (from t_{15min} to t_{2h}) and out of the site (from t_{4h} to t_{8h}) by e-Diary recording.
The following items will be recorded by the patients on the e-Diary:

- Pain relief (VRS-PAR): at t_{15min}, t_{30min}, t_{1h}, $t_{1.5h}$, t_{2h}, t_{4h}, t_{6h} and t_{8h}. Patients will be asked to answer the question *'How do you rate your pain relief?*' using a 5-point verbal rating scale (VRS), where 0 = 'no relief', 1 = 'a little (perceptible) relief', 2 = 'some (meaningful) relief', 3 = 'lot of relief', 4 = 'complete relief'.
- Pain Intensity (NRS-PI): at t_{15min}, t_{30min}, t_{1h}, $t_{1.5h}$, t_{2h}, t_{4h}, t_{6h} and t_{8h}, using the 11-point NRS.
- First intake of RM, if any.

	– Onset of analgesia: The *two-*[redacted] method will be used to assess the onset of analgesia within the first two hours (from t_0 to t_{2h}): the first stop upon the experience of "first perceptible" PAR (FPPAR) and the second stop when PAR is considered "meaningful" (MPAR). – Patient Global Evaluation (PGE): at the end of the assessment period (t_{8h}), or immediately before RM intake, if any. Patients 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'. Occurrence of any AE as spontaneous reporting and changes in CM, if any, will be collected by study staff while the patients are at the site. *Rescue medication* At any time during the 8-hour post-dose period, patients will be allowed to take RM if they have not achieved adequate pain relief after receiving the study medication; however, they will be encouraged to wait for at least 60 minutes after dosing to allow time for the study treatment effect to take place. Patients will be duly instructed by the investigator that during the 8-hour post dose period a maximum of 2 tablets of RM will be allowed, each one separated by a minimum interval of 4 hours. Patients will be also instructed to bring back the remaining RM at the End of Study visit. NOTE: After first intake of RM, patients will stop using the e-Diary including the [redacted] functionality. Only the first intake of RM will be recorded on the e-Diary. Time of each intake of RM, if any, will be recorded by the patients in a paper booklet (RM diary). The Investigator or designee will be responsible for entering RM diary data into the e-CRF. **End of Study visit (6 ± 1 days after randomisation)** – Return of e-Diary, RM diary and unused RM by patients. – RM accountability. – Physical examination. – VS measurement. – Pregnancy test (if applicable). – 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 centre to accomplish the procedures from Screening to End of study. Unscheduled surgical follow-up visits may be requested by the surgeon at an earlier timepoint; however they will not be considered as part of this study.

Efficacy endpoints	Primary endpoint: Total pain relief (TOTPAR), calculated as the weighted sum of the PAR scores (measured according to a 5-point VRS from 0=no relief to 4=complete relief), over 6 hours post-dose ($TOTPAR_6$). Secondary endpoints: – [redacted] – Percentage of patients achieving at least 50% of maximum TOTPAR over [redacted] 8 hours post-dose. – [redacted] – Percentage of patients who achieved at least 30% of PI reduction versus baseline at each pre-specified time point over the 8-hour post-dose period. – [redacted] – Time to confirmed FPPAR (time to onset of analgesia) - i.e. time to FPPAR if confirmed by experiencing MPAR – [redacted] – PGE of the study medication (measured according to a five-point VRS from 1 = poor to 5 = excellent), at 8 hours post-dose or whenever the patient uses RM. – [redacted] – Percentage of patients who required RM within [redacted] 8 hours post-dose.
Safety endpoints	– 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 physical examination, and VS, post-dose versus baseline. (NOTE: for physical examination *screening period* values will be used as baseline; for VS, the values collected during the qualification period will be used as baseline).

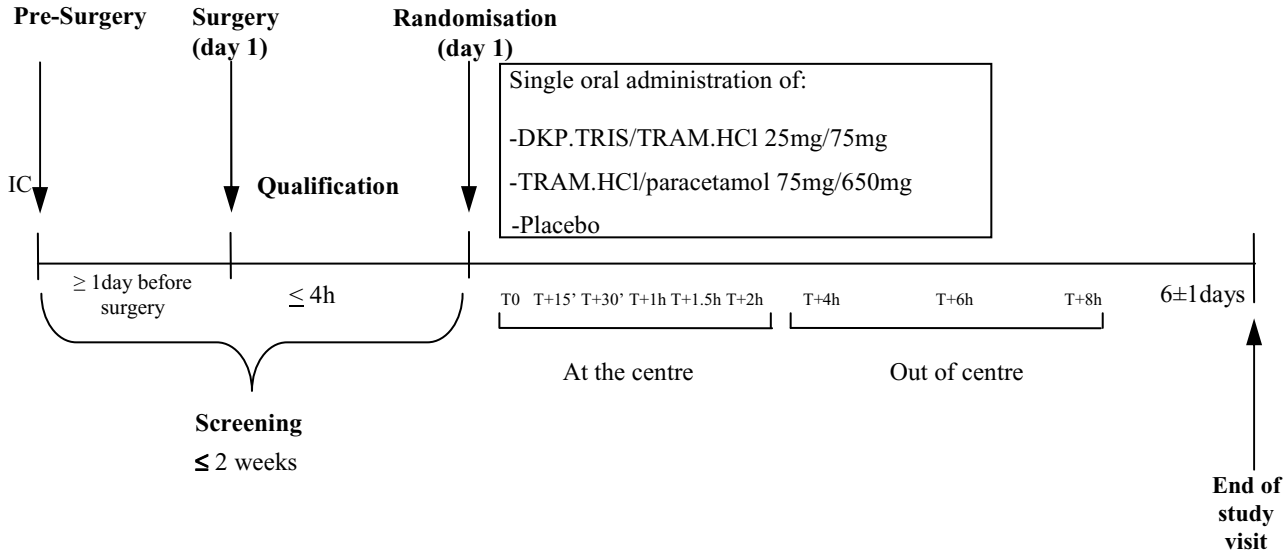
Sample size	A sample size of 230 patients per active arm is considered adequate to demonstrate the non-inferiority of DKP.TRIS/TRAM.HCl oral fixed combination compared to TRAM.HCl/paracetamol assuming a non-inferiority margin of 20%, a power of 80% and an overall significance level of 2.5 % (1-side). The mean $TOTPAR_6$ for TRAM.HCl/ paracetamol is assumed equal to 7.4 (SD 6.30). 115 patients in placebo arm are sufficient to demostrate the superiority of both TRAM.HCl/paracetamol and DKP.TRIS/TRAM.HCl vs placebo for model sensitivity. Assuming about 10% of major protocol violators, and 20% of screening failure rate a total of 640 patients need to be randomised and approximately 800 patients are expected to be screened.
Analysis populations	The following analysis populations will be considered: – Intention-to-treat (ITT) population: All patients randomised. – Safety population: All patients who have received at least one dose of the study treatment. – Per protocol (PP) population: All patients of the ITT population who did not experience relevant protocol violations related to the efficacy endpoints of primary interest.
Statistical analysis	<u>Primary efficacy analysis</u> The primary efficacy variable ($TOTPAR_6$) will be used to assess the non-inferiority of DKP.TRIS/TRAM.HCl versus TRAM.HCl/ paracetamol using analysis of covariance (ANCOVA), with treatment as main effect and adjusted for the baseline PI level 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 non-inferiority margin of 20%. In case the non-inferiority will be confirmed, the superiority of DKP.TRIS/TRAM.HCl versus TRAM.HCl/paracetamol will be tested. Non-inferiority will be tested on the PP and ITT populations, while superiority only on the ITT population. Superiority of DKP.TRIS/TRAM.HCl and TRAM.HCl/paracetamol versus placebo will be tested in order to confirm the model sensitivity on the ITT population. <u>Secondary efficacy analysis</u> $SPID_6$ will be analyzed for non inferiority with the possibility to switch for superiority analogously to the primary efficacy variable. All the other secondary efficacy variables will be descriptively analysed. The superiority for DKP.TRIS/TRAM.HCl will be tested on the secondary endpoints when applicable, through an ad hoc inferential analysis, as reported below: – NRS -PI, SPID (excluded $SPID_6$), %max SPID, TOTPAR (excluded $TOTPAR_6$), %max TOTPAR (continue variables) will be analyzed by ANCOVA model

	– PGE and VRS-PAR (categorical variables) will be analyzed by Wilcoxon rank-sum test. – Percentage of patients who required rescue medication, and percentage of patients achieving at least 30% of PI reduction, achieving at least 50% max TOTPAR, confirmed FPPAR, MPAR will be tested using a Chi²-Test. – Time to use RM, time to FPPAR, confirmed FPPAR and MPAR will be assessed using a Log-rank test. <u>Safety analysis</u> Adverse events will be coded using the MedDRA dictionary. The incidence of each TEAEs will be summarized by system organ class (SOC), preferred term (PT) and treatment. Clinically significant abnormal findings in VS and physical examination will be listed by treatment. Safety variables will be analysed only by descriptive statistics and will be run on the safety population.

<u>NOTES</u>:

- *All through the document, any mention to the dosage of 25mg dexketoprofen trometamol (DKP.TRIS) refers to the amount of dexketoprofen. The corresponding weight for the active ingredient expressed as trometamol salt (DKP.TRIS) is 36.90mg.*
- *All through the document, with DKP.TRIS/TRAM.HCl 25mg/75mg, DKP 25mg TRIS/TRAM.HCl 75mg* and *DKP+TRAM is made reference to dexketoprofen 25mg trometamol/tramadol hydrochloride 75mg fixed dose combination.*

2.1 SCHEMATIC STUDY DESIGN



2.2 STUDY FLOW- CHART

Study procedures	***Screening[a]***		***Randomisation, treatment administration and efficacy assessment period***									***End of Study***
	Prior to surgery	**Qualification (day 1)**	**At the centre (day 1)[h]**						**Out of centre (day 1)[i]**			**(6± 1 days after randomisation)**
			T-0 h	**T+15'**	**T+30'**	**T+1h**	**T+1.5h**	**T+2h**	**T+4h**	**T+6h**	**T+8h**	
Check of Informed consent[b]	X											
Demographics and Medical History	X											
Inclusion / Exclusion criteria	X	X										
Physical Examination	X											X
Vital sign (BP, HR)	X	X										X
Safety Laboratory Tests	X											
Pregnancy test (if applicable)	X	X[c]										X
e-Diary Instruction	X											
e-Diary dispensing & testing of its main functions		X										
Randomisation to treatment and Dosing			X									
PI assessment (NRS)[g]		X[d]	X[e]	X	X	X	X	X	X	X	X	
PAR assessment (VRS)[g]				X	X	X	X	X	X	X	X	
Patient's Global Evaluation											X[f]	
FPPAR and MPAR[g]			←	**As soon as they are experienced**				→				
Dispensing of RM and RM diary			X									
RM and RM diary Return / Accountability												X

Study procedures	***Screening***[a]		***Randomisation, treatment administration and efficacy assessment period***									***End of Study***
	Prior to surgery	**Qualification (day 1)**	**At the centre (day 1)**[h]						**Out of centre (day 1)**[i]			**(6± 1 days after randomisation)**
			T-0 h	**T+15'**	**T+30'**	**T+1h**	**T+1.5h**	**T+2h**	**T+4h**	**T+6h**	**T+8h**	
Return of e-Diary												X
AEs/CM recording	X	X	**While patients are at site**									X

[a] The entire screening period, including the pre-surgery evaluations, the surgical procedure and the qualification period, must be completed within 2 weeks prior to randomisation
[b] IC must be signed before any other study procedure is performed
[c] To be repeated on day 1 before randomisation if not performed the day before as screening procedure
[d] NRS-PI $\geq$ 4 is required for randomisation
[e] NRS-PI at T_0 is recorded as baseline PI
[f] Or immediately before RM intake
[g] To be completed upon RM intake, if any
[h] E-Diary recording is allowed within a ±3 minutes time window at T+15', T+30', T+1h, T+1.5h and T+2h
[i] E-Diary recording is allowed within a ±10 minutes time window at T+4h, T+6h and T+8h

3. INVESTIGATOR(S) AND STUDY ADMINISTRATIVE STRUCTURE

Co-ordinating Investigator	[redacted]

Sponsor	**Menarini Ricerche S.p.A.** **Clinical Research Department** Via Sette Santi, 1 50131 Florence, Italy
Corporate Director of Clinical Research / Sponsor's Representative	[redacted]

Clinical Research Physician	[redacted]
Study Manager	[redacted]
Biostatistician	[redacted]
Data Manager	[redacted]

Sponsor's Pharmaceutical Manufacturer of the IMP	**A. Menarini Research & Business Service GmbH Pharmaceutical Development Department** Glienicker Weg 125 D-12489 Berlin, Germany
Head of the Pharmaceutical Development Department	[redacted]
Packaging, Labelling, and Distribution of the IMP	[redacted]

Sponsor's Pharmacovigilance Unit	[redacted]
Drug Safety Manager	[redacted]

Quality Assurance	[redacted]
Head of Quality Assurance & GXP Compliance	[redacted]

CRO	[redacted]
Vice President Operations – General Partner	[redacted]

4. TABLE OF CONTENTS

4.1 GLOSSARY

ß-HCG	ß-Human Chorionic Gonadotropine
ADR	Adverse Drug Reaction
AE	Adverse Event
ALAT	Alanine Aminotransferase
a.m.	From Latin *ante meridiem*, before-noon
ANCOVA	Analysis of Covariance
ASA	American Society of Anaesthesiologists
ASAT	Aspartate Aminotransferase
AUC	Area Under the Curve
BDRM	Blind Data Review Meeting
BOCF	Baseline Observation Carried Forward
BP	Blood Pressure
CA	Competent Authority
CI	Confidence Interval
CM	Concomitant Medication
C_{max}	Maximum Plasma Concentration
CPK	Creatine Phosphokinase
CRF	Case Report Form
CRO	Clinical Research Organisation
COX	Cyclooxygenase
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
DKP.TRIS	Dexketoprofen Trometamol
DSM	Drug Safety Manager
DSUR	Development Safety Update Report
EC	Ethics Committee
ECG	Electrocardiogram
e-CRF	Electronic Case Report Form
e-Diary	Electronic Diary
FPPAR	First Perceptible Pain Relief
G6PD	glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
Hb	Haemoglobin
HCT	Haematocrit
HR	Heart rate
IASP	International Association for the Study of Pain
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
i.m.	Intramuscular
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
ITT	Intention-to-treat
i.v.	Intravenous
IxRS (IVRS/IWRS)	Interactive Voice/Web Response System
LDH	Lactate Dehydrogenase
LOCF	Last Observation Carried Forward
M1	O-demethyltramadol
MAO	Monoamine oxidase
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MIA	Monosodium Iodoacetate

MPAR	Meaningful Pain Relief
N	Number of Non-missing Observations
NRS	Numerical Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
PAR	Pain Relief
PCA	Patient Controlled Analgesia
PGE	Patient Global Evaluation
PI	Pain Intensity
PID	Pain Intensity Difference
PK	pharmacokinetics
PP	Per-protocol
PT	Preferred Term
PTT	Partial Thromboplastin Time
QA	Quality Assurance
RBC	Red Blood Cell
RM	Rescue Medication
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPID	Sum of Pain Intensity Differences
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAEs	Treatment Emergent Adverse Events
$t_{1/2,\beta}$	Elimination half-life
t_{max}	Time to Maximum Plasma Concentration
TMF	Trial Master File
TOTPAR	Total Pain Relief
TRAM.HCl	Tramadol Hydrochloride
VRS	Verbal Rating Scale
VS	Vital Signs
WBC	White Blood Cell

5. ETHICAL AND LEGAL ASPECTS

5.1 GENERAL ASPECTS

This study will be carried out in compliance with the study protocol, the recommendations on biomedical research on human subjects of the Declaration of Helsinki[1], International Conference of Harmonisation, and national requirements of the participating countries.

The Sponsor has contracted the Contract Research Organisation (CRO) to perform some of the Sponsor's trial related duties and functions like site selection and monitoring. Medical monitoring, safety management, data management, statistical analysis and medical writing will be performed by the Sponsor. The ultimate responsibility for the quality and the integrity of the study resides with the Sponsor. The study will be conducted in agreement with Sponsor's or CRO's Standard Operating Procedures' (SOP) requirements as agreed.

All clinical work conducted under this protocol is subject to GCP rules. This includes audits/inspections by the Sponsor and/or its delegate (e.g. CRO), and/or by national/international Health Authority representatives at any time. All Investigators must agree to the audits/inspection of the study site, facilities, and of study-related records by the Health Authority representatives and/or by the Sponsor, and/or its delegates, which must be performed in accordance with national laws concerning personal data protection.

5.2 INDEPENDENT ETHICS COMMITTEE AND LEGAL REQUIREMENTS

Before starting the study in a study site, study protocol and relevant documentation must be submitted to and approved by the Competent Authorities (CAs) and the Independent Ethics Committees (IEC) of the participating Countries/Centres.

In addition, all local national legal requirements for the conduct of a clinical study have to be followed prior to the start of the study. The CAs and IECs of the participating centres will be informed about any changes in the study protocol, the end of the study, or the premature study termination as appropriate, and within the requested time period.

5.3 PATIENT INFORMATION AND DECLARATION OF CONSENT

Before any study-related procedures may be performed, informed consent must be obtained from the patient by means of a signed declaration.

The Informed Consent Form (ICF) must be approved in the corresponding local language and in accordance with local laws and regulations by the IEC prior to be submitted to the patient.

In the patient information leaflet, patients will be given information and fully comprehensive explanation in easily understandable terms of the study procedures, regarding the benefits, restrictions, discomforts, and risks in taking part in the study, the properties of the Investigational Medicinal Product (IMP), the method of assignment to treatments, and any medically accepted and readily available treatment other than the IMP.

Patients will also be informed about the measures taken to ensure their confidentiality according to the pertinent legislation.

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. The process of obtaining the ICF has to be documented in the source documents.

If a protocol amendment would affect the terms of the ICF, it will be revised to reflect the protocol change and submitted to IEC for approval. The Investigator will ensure that this new ICF is signed by all patients who subsequently enter in the study and those who are currently in the study, before the changes take effect on their participation in the trial.

5.4 PATIENT INSURANCE

For patients participating in the study, the Sponsor Menarini Ricerche S.p.A. has stipulated an insurance policy in accordance with local regulatory requirements.

Details on the insurance company, the insurance number and conditions will be reported in the ICF and/or provided as a separate document, in accordance with national requirements.

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).

5.5 DOCUMENTATION OF STUDY-RELATED DATA AND RECORD RETENTION

It is the responsibility of the Investigator to document all study-related data for each patient and record them in a case report form (CRF). For this study, an electronic CRF (e-CRF) will be used. The Investigator has to guarantee the accuracy of the documented data and has to comment any missing or spurious data.

In addition to the e-CRF the Investigator will maintain adequate records that fully document the participation of the patient in the clinical study including the study assessments (patient source data documentation). Details on the source data documentation are provided in section 10.3. As required by ICH-GCP guidelines, the Investigator will keep patients' records and essential documents until at least two years after the last approval of a marketing application in an ICH region, or until there are no pending or contemplated marketing applications in an ICH region, or at least two years have elapsed since the formal discontinuation of clinical development of the IMP.

Patients' data (*e.g. e-CRFs, safety laboratory data*) have to be archived for the same period of time. These documents should be retained for a longer period however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. No study documents should be destroyed without prior written agreement between Sponsor and Investigator. Should the Investigator wish moving the study record to another location, he/she must notify the Sponsor in writing.

Details on the archiving of electronic documents/data are provided in section 12.1.

5.6 CONFIDENTIALITY

By signing the study protocol, the Investigator affirms that any information provided by the Sponsor will be maintained in confidence, and that such information will be divulged to IECs or CAs only under an appropriate understanding of confidentiality with such a committee or institution.

In order to maintain the patient's confidentiality, all data collected by the Investigator will be recorded pseudonymously in the e-CRF. Patient's data will be identified by a unique patient number. The Investigator agrees that within national regulatory restrictions and ethical considerations, representatives of the Sponsor, any regulatory agency, and IEC may consult study source documents in order to verify data in the e-CRF. Patient medical records pertinent to the study will be reviewed by the study monitor to assure adequate source documentation, accuracy, and completeness of e-CRFs. The review will be conducted in accordance with relevant SOPs and with strict adherence to professional standards of confidentiality, GCP, and the relevant data protection legislation.

5.7 PROTOCOL MODIFICATIONS

The protocol must be read thoroughly by everybody whom the information therein concerns and the instructions must be exactly followed.

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, i.e. 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 IECs and the CAs in the participating countries have to approve these amendments before implementation unless urgent safety measures need to be implemented (see section 5.9).

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 IECs and the CAs 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.

5.8 STUDY COMMENCEMENT

The study can commence in an individual study site only after all prerequisites are fulfilled according to ICH/GCP guidelines, any local regulatory requirements, and the Sponsor/CRO's SOPs.

5.9 PATIENT'S SAFETY

If any event(s) related to the conduct of the study or to the IMP affects the safety of the study participants, the Sponsor and the Investigator will take appropriate urgent safety measures to protect the patients against any immediate hazard. The CAs and IECs will be informed forthwith about these new events and the measures taken.

5.10 DATA PROPERTY/PUBLICATION POLICY

All data generated in the study (e.g. e-CRFs, patient diaries, the structured data files in the clinical database system, the results of the statistical evaluation, and medical interpretation as well as the final clinical study report) are the property of Menarini Ricerche S.p.A.

It is intended that study design and main results will be published on www.clinicaltrials.gov. In addition, the results of the study may be published as scientific literature. Results may also be used in submissions to CAs. The conditions mentioned below are intended only to protect confidential commercial information (patents, etc.), and not to restrict publication.

All information concerning dexketoprofen trometamol/tramadol hydrochloride fixed dose combination –abbreviated as DKP.TRIS/TRAM.HCl- (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the investigator by Menarini Ricerche S.p.A. and not previously published) is considered confidential by Menarini Ricerche S.p.A. and will remain the sole property of Menarini Ricerche S.p.A. The investigator agrees not to use it for other purposes without written consent from Menarini Ricerche S.p.A.

Menarini Ricerche S.p.A. will use the information obtained in this clinical study in connection with the development of DKP.TRIS/TRAM.HCl and therefore may disclose it to other investigators or concerned CAs and IECs in the European Union or abroad. In order to allow for the use of information derived from this clinical study, the Investigator has an obligation to provide Menarini Ricerche S.p.A. with complete test results and all data recorded during this study.

Prior to submitting the results of this study for publication or presentation, the Investigator will allow Menarini Ricerche S.p.A. at least 60 days time to review and comment upon the publication manuscript. Menarini Ricerche S.p.A. will provide any manuscript of the results of this study at least 60 days before publishing to the authors for a complete review. In accordance with generally recognised principles of scientific collaboration, co-authorship with any Menarini Ricerche S.p.A. personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

It is agreed, that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the Investigator until Menarini Ricerche S.p.A. has reviewed/commented and agreed to any publication.

6. BACKGROUND INFORMATION

6.1 PAIN

Pain is the most common symptom for which patients seek medical attention. It can be defined as *an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage* (International Association for the Study of Pain, IASP)[2].

Pain can be either acute or chronic. Acute pain typically is associated with recent tissue injury and has a short duration. Tissue injury causes a cascade of events, including peripheral inflammation, that release various mediators into the local environment. These mediators activate the primary afferent nerves or sensitize local nerve receptors, which, in turn, can evoke changes at the level of the spinal cord, a process referred to as 'peripheral sensitization'. This process is responsible for the development of hyperalgesia beyond the damaged site. If acute pain is not properly treated, prolonged activation of the pain pathways can lead to further neurophysiologic changes collectively called 'central sensitization' which may prolong recovery and in some cases convert acute pain into a chronic condition. Proper analgesic treatment can reduce this risk[3]. Pain due to tissue damage is referred to as nociceptive. The response to nociceptor sensory input is a multifactorial process, with both central and peripheral mechanisms involved[4]. Nociceptive pain usually responds to non-steroidal anti-inflammatory drugs (NSAIDs) and opioids.

In spite of the great variety of analgesics available, the management of patients suffering from pain still continues to be inadequate[5, 6, 7]. Due to the subjective component of pain, the problems associated to a correct diagnosis or the fear of the adverse reactions associated to some drugs, patients are frequently undertreated for acute and chronic situations[2]. One study on the prevalence of post-operative pain in surgical inpatients stated that 41% of 1490 surgical patients reported moderate to severe pain despite an acute pain protocol[8].

Clinical experience has proven that in patients with moderate to severe pain, it is difficult to obtain an effective analgesia with a single drug (monotherapy) and therefore, analgesic drugs are commonly combined (multimodal analgesia) in order to obtain an optimal control of pain. Multimodal analgesia has shown its benefits in treating different kinds of acute and chronic pain in humans. However, extemporaneous combinations of available analgesics are often used empirically, without knowing the mechanism of interaction and/or the best dose ratio of the analgesics to be combined in order to achieve optimal efficacy and safety[9, 5, 6, 7].

6.2 INVESTIGATIONAL MEDICINAL PRODUCT: DEXKETOPROFEN TROMETAMOL AND TRAMADOL HYDROCHLORIDE FIXED COMBINATION

Menarini Ricerche is developing a combination of DKP.TRIS and TRAM.HCl, two analgesics with different mechanism 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 which have been present in the market of most European countries for a very long time.

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

(i) DKP.TRIS and TRAM.HCl have different mechanisms of action; the former exerts its antinociceptive activity mainly at the peripheral level, whereas the latter is a centrally acting analgesic;

(ii) DKP.TRIS and TRAM.HCl have different pharmacokinetic profiles; their combination is expected to be characterized both by quick onset (typical of DKP.TRIS) and long duration (peculiar to TRAM.HCl) of the analgesic effect.

This pharmacodynamic and pharmacokinetic rationale is supported by preclinical and clinical evidence. Data on the single components are reported below.

Dexketoprofen trometamol

DKP.TRIS 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[10, 11].

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 post-administration, with analgesic effect persisting for 4 to 6 hours[12, 13, 14 ,15, 16, 17].

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[18].

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})[19].

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[18].

Oral DKP.TRIS (as 12.5mg and 25mg 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 12.5mg every 4-6 hours or 25mg every 8 hours. The total daily dose should not exceed 75mg[20].

DKP.TRIS is also available on the market as a 50mg/2ml injectable formulation –to be administered either by intramuscular (i.m.) or by intravenous (i.v.) route–, which is indicated for the symptomatic treatment of acute pain of moderate to severe intensity, such as post-operative pain, renal colic and low back pain. The recommended dose is 50mg every 8 - 12 hours. If necessary, the administration can be repeated 6 hours apart. The total daily dose should not exceed 150mg[21].

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][22, 23].

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[22 23] . The mean absolute bioavailability is approximately 70%, irrespective of the concomitant intake of food. Following a single oral dose administration of TRAM.HCl 100mg 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[22 23].

Oral TRAM.HCl is currently authorised over 90 countries as 50mg to 400mg different formulations (capsules, tablets and extended-release formulations). It is indicated for the treatment of moderate to severe pain. The start dose in case of acute pain is 100mg, and the recommended unitary dose is between 50 and 100mg not taken more frequently than every 4 hours, with a maximum of 400mg/day[23].

6.2.1 Data on the co-administration of dexketoprofen trometamol and tramadol hydrochloride

6.2.1.1 Pre-clinical studies

Previous pre-clinical studies performed in mice showed that the co-administration of DKP.TRIS with TRAM.HCl produces an additive-synergistic anti-nociception, which seems to be modulated by opioid receptors. The results also showed that DKP.TRIS antagonises the effects of TRAM.HCl on the inhibition of gastrointestinal transit, a fact that could be clinically beneficial since the incidence or intensity of constipation on the TRAM.HCl treated patients could diminish[24].

The analgesic effects of the oral co-administration of DKP.TRIS with TRAM.HCl in comparison with the same drugs administered individually have also been investigated in rats on a knee-osteoarthritis model induced by intra-articular injection of monosodium iodoacetate (MIA). The co-administration of DKP.TRIS with TRAM.HCl demonstrated a statistically significant improvement of analgesia and a more prolonged effect as compared to the single drug administration[25].

6.2.1.2 Published data from non-sponsored clinical studies

Published clinical evidence particularly supports the rationale for developing a combination of an analgesic opioid such as TRAM.HCl and a NSAID.

A review on the multimodal analgesia for post-operative pain control showed that neither opioids nor NSAIDs alone can have an effective analgesic effect without producing side effects such as nausea, vomiting, sedation and intestinal bleeding. The same review reported that most clinical studies (either double or single blind) testing the association of NSAIDs and opioids showed that patients experience lower pain scores, need fewer analgesics, and have a prolonged time to requiring analgesics after surgery[26].

The results of two clinical studies evaluating the effects of oral DKP.TRIS co-administered with TRAM.HCl i.v. via a Patient Controlled Analgesia (PCA) device on post-operative pain showed that DKP.TRIS provided a significant analgesic benefit and reduced post-operative TRAM.HCl consumption. Study objectives included the evaluation of the efficacy of two different multimodal analgesia protocols (with or without oral DKP.TRIS in addition to standard-practice TRAM.HCl i.v.) in terms of post-operative pain relief, TRAM.HCl consumption during PCA and side effects after abdominal hysterectomy (n = 50) or total hip replacement surgery (n = 36). In both studies, the two tested analgesia protocols including TRAM.HCl in monotherapy or in combination with DKP.TRIS were effective in relieving pain with no significant differences between groups in sedation scores, adverse effects or patient satisfaction. It was concluded that the administration of DKP.TRIS provided a significant analgesic benefit and decreased the opioid requirements in the treatment of moderate to severe post-operative pain[27, 28].

In addition, in a double-blind randomised clinical trial in order to assess the efficacy of ketoprofen (the racemic drug of dexketoprofen) in association with TRAM.HCl in post-operative pain treatment after major abdominal surgery, it was shown that the total dose of TRAM.HCl needed to obtain a better analgesic quality was lower in the group treated with TRAM.HCl combined with ketoprofen (193mg/24h i.v.) than in the group treated only with TRAM.HCl (235mg/24h i.v.). It was concluded that ketoprofen, used as an adjuvant to TRAM.HCl, significantly improved the quality of post-operative analgesia after major abdominal surgery[29].

6.2.1.3 Post-marketing clinical experience

IMS Health data on DKP.TRIS (Enantyum®) non-hospital prescriptions in Spain in 2009 for the two marketed oral forms (tablets and sachets) and for the injectable formulation showed that DKP.TRIS was prescribed concomitantly with TRAM.HCl in around 125.000 cases (oral forms) and 6.400 cases (injectable formulation) over a total of 5.695.476 prescriptions.

These numbers indicated that the use of the two 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, which supports the medical need for the development of a fixed-dose combination of these two products.

6.2.2 Clinical development of dexketoprofen trometamol and tramadol hydrochloride fixed combination

The clinical development of the the DKP.TRIS/TRAM.HCl fixed-combination started with a phase I safety and pharmacokinetics (PK) study (DEX-TRA-PK)[30], aimed at investigating the potential drug-drug interactions between the products as well as their tolerability when concomitantly administered as a single oral dose to healthy subjects. The study results indicated that there was no drug-drug interaction between DKP.TRIS and TRAM.HCl and that the concomitant administration was well tolerated. A phase II dose-finding study (DEX-TRA-02)[31] [32]was performed in the most frequently used model of acute nociceptive pain of moderate-severe intensity (impacted third mandibular molar tooth extraction), aimed at evaluating the analgesic efficacy and safety of DKP.TRIS (12.5mg and 25mg) and TRAM.HCl (37.5mg and 75mg) given as 4 different combinations and as single components. Results from DEX-TRA-02 allowed for the selection of DKP.TRIS/TRAM.HCl 25mg/75mg as the optimum combination of doses then evaluated in the subsequent phase III registration studies.

DEX-TRA-04 [33] and DEX-TRA-05[34] were two phase III registration studies aimed at evaluating the analgesic efficacy and safety of the DKP.TRIS/TRAM.HCl 25/75mg oral fixed-dose combination in comparison with each single component (tramadol given at a higher dose, 100mg), 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 study results provided robust evidence of the superiority of DKP.TRIS/TRAM.HCl 25mg/75mg over the single components in the management of moderate to severe acute pain.

6.2.2.1 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 18-54 years, who had previously tolerated a test dose of DKP. TRIS 12.5mg + TRAM.HCl 50mg), divided in 3 cohorts of 10 subjects, were assigned to receive, according to a cross-over design, one single oral dose of DKP.TRIS 25mg, TRAM.HCl 100mg 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 (PK) assessment. Standard safety parameters were measured during each of the 3 study sessions, with a final safety follow-up visit performed 7-10 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 100mg and DKP.TRIS 25mg when concomitantly orally administered to healthy subjects. Moreover, the concomitant administration was well tolerated without raising any safety concerns.

6.2.2.2 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 (12.5mg and 25mg) and TRAM.HCl (37.5mg and 75mg) 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 400mg) 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)[2].

The design included a total of 10 balanced treatment arms, with the 4 combinations of DKP.TRIS/TRAM.HCl (12.5mg/37.5mg, 12.5mg/75mg, 25mg/37.5mg and 25mg/75mg), the 4 corresponding single treatments, placebo and ibuprofen 400mg.

A total of 611 patients (247 males and 364 females, aged 18-64 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 (RM) consisting of paracetamol (1g, every 6-8 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 post-dosing period, the patient global evaluation (PGE) at the end of the assessment period and the use of 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 (VS), 12-lead ECG, and laboratory safety tests post-dose versus baseline. Recording and monitoring of 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 25mg/75mg 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 12.5mg/37.5mg) over 8 and 12 hours.

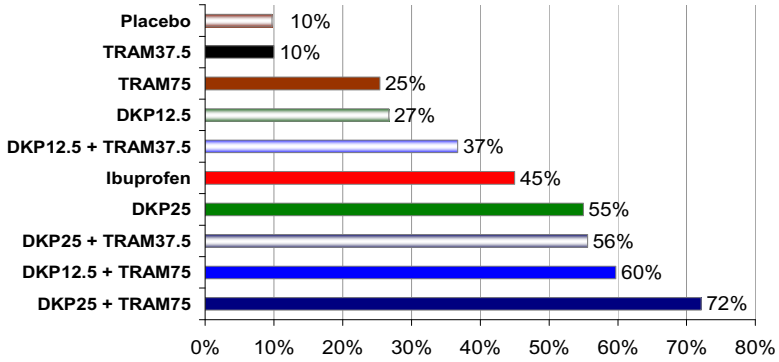


Figure 1: Primary Endpoint - Percentage of responders (achievement of at least 50% max TOTPAR) over 6 hours; max TOTPAR corresponded to the theoretical maximum weighted sum of the PAR scores, according to a 5-point VRS (0 = 'none' to 4 = 'complete'); ($p < 0.0001$ for each comparison; except $p = 0.0009$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

The analysis of SPID (Sum of Pain Intensity Differences), 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 25mg/75mg. The time to RM was significantly longer for all combinations than for placebo, with DKP.TRIS/TRAM.HCl 12.5mg/75mg and DKP.TRIS/TRAM.HCl 25mg/75mg 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 12.5mg/75mg, DKP.TRIS/TRAM.HCl 25mg/37.5mg and DKP.TRIS/TRAM.HCl 25mg/75mg than in the placebo group (46.8%, 39.7% and 37.7% respectively versus 72.6%), with the DKP.TRIS/TRAM.HCl 25mg/75mg group presenting the lowest percentage. The difference was still significant for DKP.TRIS/TRAM.HCl 25mg/75mg 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 25mg/75mg 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 25mg/75mg, DKP.TRIS/TRAM.HCl 12.5mg/75mg and DKP.TRIS/TRAM.HCl 25mg/37.5mg 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 25mg/75mg 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 25mg/75mg 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 25mg/75mg 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 25mg/75mg to be administered every 8 hours.

6.2.3 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 25mg/75mg oral fixed-combination in comparison with the single components (dexketoprofen 25mg and tramadol 100mg) 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 DEX-TRA-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 25mg/75mg, dexketoprofen 25mg, tramadol 100mg 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 25mg/75mg, dexketoprofen 25mg or tramadol 100mg). 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 500mg, with a maximum recommended daily dose of 2g) 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).

6.2.3.1 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 $SPID_8$, Fig. 2) confirmed the superiority of dexketoprofen/tramadol over the single components (mean [SD]: 242 [139] for dexketoprofen/tramadol versus 185 [139] for dexketoprofen and 157 [151] for tramadol; $p<0.001$ 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 PP population confirmed the primary efficacy results.

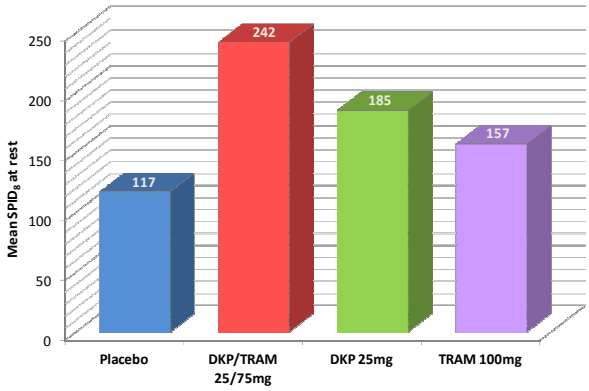


Figure 2 - Mean $SPID_8$ (Primary Endpoint). PI measured on a 0-100 VAS, with the left end labeled "no pain" and the right end labeled "worst possible pain".

There was statistical evidence favouring dexketoprofen/tramadol 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 dexketoprofen/tramadol 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 dexketoprofen/tramadol 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 dexketoprofen/tramadol compared to the single agents. Dexketoprofen/tramadol 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 dexketoprofen/tramadol than with the single agents. Results were mantained over 48 hours and overall during the multiple-dose phase, but the differences did not reach statistical significance.

Dexketoprofen/tramadol 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 mantained for the multiple dose phase of the study.

Overall, 76 (13%) patients reported a total of 100 adverse reactions (ADRs), of which 51 were mild, 42 were moderate and seven 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; nine events), platelet count increased (1.3% patients; eight events) and

blood lactate dehydrogenase increased (1.0% patients; six events). The dexketoprofen/tramadol group presented a lower incidence of ADRs (9.4% patients) in comparison with the dexketoprofen (15% patients) and tramadol groups (13% patients). Overall, 11 (1.8%) patients reported a total of 15 serious adverse events (SAEs), of which only one (psychotic disorder; in the dexketoprofen/tramadol 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 dexketoprofen/tramadol combination showed a safety profile fully in line with that previously known for the single agents.

6.2.3.2 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, Fig. 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.

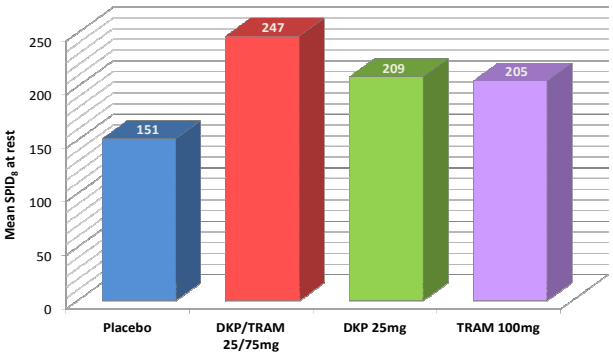


Figure 3 - Mean $SPID_8$ (Primary Endpoint). PI measured on a 0-100 VAS, with the left end labeled "no pain" and the right end labeled "worst possible pain".

When assessed by PI (mean PI, mean SPID, mean % max SPID, response to treatment), dexketoprofen/tramadol was more effective than either dexketoprofen monotherapy or tramadol

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 dexketoprofen/tramadol group when compared to the single agents, although the differences did not reach statistical significance.

Similarly, the highest PGE scores were reported in the dexketoprofen/tramadol 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 dexketoprofen/tramadol compared with dexketoprofen monotherapy and tramadol 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 dexketoprofen/tramadol group than in the dexketoprofen group and in the tramadol group.

The worst pain score whilst moving was slightly lower on average for the dexketoprofen/tramadol group than for the dexketoprofen group and the tramadol 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 dexketoprofen/tramadol group presented a lower incidence of ADRs (2.8% patients) in comparison with the dexketoprofen group (4.7% patients) and the tramadol group (5.1% patients).

Two patients reported a total of five serious ADRs. One patient in the dexketoprofen group experienced duodenal ulcer. Another patient in the dexketoprofen/tramadol 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 HR, BP, 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 dexketoprofen/tramadol 25mg/75mg 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.

6.2.4 DEX-TRA-06: Phase IIIb new study in dental pain model

The present phase IIIb study is aimed to evaluate the analgesic efficacy, safety and tolerability of DKP.TRIS/TRAM.HCl 25mg/75mg in comparison with TRAM.HCl /paracetamol 75mg/650mg, an oral fixed-combination indicated in the treatment of moderate to severe acute pain and already present in the market.

The surgical removal of impacted lower third molar is a well-recognised model of moderate to severe pain commonly used in the development of analgesic drugs (it has already been used in DEX-TRA-02 study) that offers considerable advantages from a methodological point of view: a) the incidence of such procedures in young adults is relatively high and the patient population is healthy and generally free from complications; b) the surgical procedure is fairly uniform and the nature and extent of tissue trauma are limited and comparable among patients; c) the postoperative pain typically begins within 1 to 3 hours after surgery, ranges from moderate to severe in intensity and requires the use of analgesics. These characteristics reduce variability in the study population and allow reasonable sample size to detect differences between treatments[35 36 37 38 39]

6.3 RISK-BENEFIT ASSESSMENT

In this study, patients will receive one single oral dose of DKP.TRIS/TRAM.HCl 25mg/75mg, TRAM.HCl/paracetamol 75mg/650mg or placebo (in a 2:2:1 ratio).

RM consisting of ibuprofen 400mg (a maximum of 2 tablets, each one separated by a minimum interval of 4 hours) will be available on request during the 8-hour post-dose period. Ibuprofen 400mg is a safe and effective drug for the treatment of dental and post-operative pain (Ibuprofen SmPC)[40].

According to the results from the previous phase I to III studies (§ 6.2.2 and § 6.2.3), dexketoprofen/tramadol 25mg/75mg is expected to provide adequate pain relief for the participating patients without raising any safety concerns. In addition, both dexketoprofen and tramadol will be administered within the higher unitary dose (25mg and 100mg, respectively) and well below the maximum daily dose (75mg and 400mg, respectively) recommended by the respective authorised Summary of Product Characteristics (SmPC)[20, 23].

The selected active comparator (TRAM.HCl/paracetamol 75mg/650mg) is indicated for the symptomatic treatment of moderate to severe pain. According to the authorised[41] SmPC, an initial dose of 75mg/650mg is recommended, with additional doses to be taken as needed, not exceeding 300 mg tramadol and 2600 mg paracetamol per day.

The inclusion of the placebo arm is considered appropriate from the ethical point of view, taking into account the self-limiting nature of the post-operative dental pain, the single-dose nature of the study and the availability of RM.

None of the study procedures or requested examinations (such as blood draws) is associated with any specific risks. AEs, if any will be recorded during the entire study period. Upon discharge from the study site, patients will be instructed to contact the site immediately in case of any medical emergency.

7. STUDY OBJECTIVES

7.1 PRIMARY OBJECTIVE

To assess the comparability of DKP.TRIS/TRAM.HCl and TRAM.HCl/paracetamol in terms of analgesic efficacy on moderate to severe pain following impacted lower third molar extraction.

7.2 SECONDARY OBJECTIVES

To confirm the safety and tolerability profile of DKP.TRIS/TRAM.HCl following single dose administration.

8. INVESTIGATIONAL PLAN

8.1 OVERALL STUDY DESIGN AND PLAN DESCRIPTION

DEX-TRA-06 is designed as a multicentre, randomised, double-blind, double-dummy, parallel-group, placebo and active-controlled, single dose, phase IIIb study, intended to be conducted in approximately 20 sites among Europe and Turkey.

The study design includes a total of 3 treatment arms, with a 2:2:1 randomisation ratio:

- DKP.TRIS/TRAM.HCl
- TRAM.HCl/paracetamol
- Placebo

Male or female patients, aged more than 18 years, scheduled to undergo surgical extraction (under local anaesthesia) of at least one impacted lower third molar and who are otherwise healthy will be enrolled in the study.

Upon completion of the surgical extraction, those patients experiencing moderate to severe pain (Numerical Rating Scale, NRS ≥4) within 4 hours after the end of surgery will be considered eligible to progress with randomisation and to receive one single oral dose of the assigned study treatment.

Rescue medication (RM) consisting of ibuprofen 400mg (a maximum of 2 tablets, each one separated by a minimum interval of 4 hours) will be available on request during the 8-hour post-dose period.

The analgesic efficacy evaluation will be based on patients' e-Diary scores of pain intensity (PI) and pain relief (PAR) at pre-defined intervals during the 8-hour post-dose period; the patient global evaluation (PGE) of the study medication at the end of the assessment period; the time to onset of the analgesic effect within two hours post-dose and the first use of RM. The safety evaluation will include a physical examination, vital signs (VS) and recording of adverse events (AEs).

The individual study participation will have duration of approximately 3 weeks, encompassing:

- Screening period, for study eligibility assessment (within 2 weeks prior to randomisation), including the pre-surgery procedures to be completed at least one day prior to surgery and ending with the 4-hour qualification post-surgery.
- Randomisation and treatment administration (day 1, t_0) followed by a 8-hour pain and analgesic effect assessment period as follows:
  - from t_0 to t_{2h}, at the study centre.
  - from t_{2h} to t_{8h}, out of the study centre.
- End of study visit (6 ± 1 days after randomisation).

The design contemplates a sample size of 640 randomised patients. It is anticipated that approximately 800 patients will be needed to be screened in order to obtain 640 randomised patients, under the assumption that approximately 20% of the screened patients will not satisfy the eligibility criteria for randomisation. The enrolment will be competitive.

The overall clinical phase is planned to start in 1H 2016 and to be completed within the Q4 2016.

8.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

The DEX-TRA-06 study has been designed to compare the efficacy between dexketoprofen/tramadol 25mg/75mg and TRAM.HCl/paracetamol on moderate to severe pain following impacted lower third molar extraction.

Tramadol/paracetamol has been selected as the active control as it has proven to be an effective analgesic for the treatment of moderate to severe painful conditions, such as postoperative dental pain, and it appears to be generally well tolerated[42].

A placebo arm has been included due to the high and variable placebo response rate, and is intended to validate the model of pain.

A single-dose trial design has been selected since it is regarded as sensitive and precise, constituting the cornerstone of the determination of analgesic efficacy [43, 44].

The parameters selected for the efficacy evaluation (PI, PAR, PGE, time to onset of analgesia and use of RM) are typical of studies with analgesics [35, 45, 46, 47, 48, 49].

Ibuprofen 400mg has been chosen as RM because, in accordance with published literature, it is a reference standard for the treatment of dental pain [50, 51].

The baseline observation carried forward (BOCF) method[52] will be applied after use of RM in order to minimize the impact of its use on efficacy assessments.

8.3 SELECTION OF STUDY POPULATION

After providing informed consent, the eligibility of the patients to enter this study will be assessed based on the inclusion and exclusion criteria, which will be checked during the screening period with a re-checked to be done after the surgery during the qualification period.

Patients will be included only if they meet all of the inclusion criteria (§ 8.3.1), do not meet any of the exclusion criteria (§ 8.3.2) and if they agree to accept the restrictions that come with participating in this study (§ 8.3.3).

8.3.1 Inclusion criteria

To be eligible for this study, EACH of the following criteria must be satisfied:

1. Properly executed written informed consent.
2. Male or female patients aged more than 18 years.

3. Scheduled for outpatient surgical extraction -under local anaesthesia (i.e. 2% lidocaine with 1:80,000 epinephrine) - of lower third molar teeth, with at least one of which fully or partially impacted in the mandible requiring bone manipulation (e.g. level B or C plus class II or III of the Pell-Gregory scale).
4. Females participating in the study must be either:
   - Females of non-childbearing potential, defined as any woman who had undergone surgical sterilization or is more than 2 years post-menopausal;
   - Females of childbearing potential provided that they have a negative pregnancy test at baseline (screening and qualification period) and are routinely using an effective method of birth control resulting in a low failure rate (i.e. hormonal contraception, intrauterine device, condoms in combination with a spermicidal cream, male partner sterilization –vasectomy– or total sexual abstinence).
5. Mentally competent, able to understand and give written informed consent prior to study entry.
6. Compliant to undergo all visits and procedures scheduled in the study, including recording of pain assessments on the electronic diary (e-Diary) as required by protocol.

After surgery, patients will be eligible to progress with randomisation ONLY if the following criterion is also met:

7. Pain of at least moderate intensity in the first 4 hours after the end of surgery (NRS score $\geq$ 4).

8.3.2 Exclusion criteria

To be eligible for this study, NONE of the following criteria must be satisfied:

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, concomitant medication (CM) and concurrent systemic diseases.
2. Clinically significant abnormalities in the vital signs (VS) and / or safety laboratory tests, as per investigator's judgement.
3. History of allergy or hypersensitivity to the study treatments, RM or to any other NSAIDs, opioids and acetyl salicylic acid.
4. History of peptic ulcer, gastrointestinal disorders by NSAIDs or gastrointestinal bleeding or other active bleedings.
5. History of severe asthma.
6. Moderate to severe renal dysfunction, severe hepatic dysfunction or severe cardiac dysfunction.
7. Coagulation disorders.
8. History of, or current epilepsy.
9. Patients with Crohn's disease or ulcerative colitis.

10. Patients using and not suitable for withdrawing analgesics, , within 12 hours before surgery (5 days prior to the surgery day in case of COX-2 inhibitors) and for 8 hours post-dose [for analgesics other than those specified in the protocol (namely study treatments and RM)].
11. Patients using and not suitable for withdrawing alcohol, sedatives (e.g. benzodiazepines) and hypnotic agents within 12 hours before surgery and for 8 hours post-dose.
12. Chronic opioid treatment (major opioids and tramadol).
13. Patients using and not suitable for withdrawing the following prohibited medications, within 48 hours or 5 half-lives (whichever the longer) prior to the start of surgery and for 24 hours post-dose:
    - Anticoagulants, thrombolytic and antiplatelet agents
    - Corticosteroids (with the exception of inhalers or topical agents);
    - Monoamine oxidase (MAO) inhibitors (a minimum of 14 days must elapse prior to the start of surgery);
    - Antiepileptics;
    - Antipsychotics;
    - Serotonin reuptake inhibitors and tricyclic antidepressants;
    - Lithium;
    - Methotrexate;
    - Antibacterial sulfonamides.
14. Participation in other clinical studies in the previous 4 weeks.
15. 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).
16. 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.
17. Pregnant and breastfeeding women. NOTE: a pregnancy test will be performed to all women of childbearing potential at Screening and another one on the day of surgery prior to randomisation.

After surgery, <u>patients will not be eligible to progress with randomisation if the following criterion is also met:</u>

18. Surgical complication that, in the opinion of the Investigator, advises against their inclusion in the study.

8.3.3 Study restrictions

Patients will be asked to adhere to the following study restrictions during their study participation, which are also listed and explained in the ICF:

- Patients must attend the site in fasting conditions on the day of laboratory tests.
- On the morning of Day 1, patients might have a light breakfast no less than 2 hours before surgery. After surgery, they will not be allowed food for at least 2 hours post-dose.
- Intake of alcohol is restricted within 12 hours before surgery and for 8 hours post-dose.
- Smoking and intake of caffeine are restricted within the 2 hours before surgery and for 8 hours post-dose.
- Local application of ice is not permitted during the 8-hour post-dose period.

For study restrictions on concomitant medication, refer to § 8.5.6.

NOTE: During the study, antibiotic prophylaxis is permitted, at the Investigator's discretion. The use of alcohol-free mouthwashes with chlorhexidine or similar agents is also allowed.

8.3.4 Withdrawal of patients from therapy or assessment

Participation in the study is strictly voluntary and patients have the right to withdraw from the study at any time without explanation. This will not affect their rights for future medical care. Patients may also be withdrawn at the Investigator's discretion or at specific Sponsor's request at any time. In the event that the patient withdraws from the study for whatever reason, the Investigator must be informed immediately and the date, reasons, and circumstances for premature discontinuation will be documented in the corresponding section of the e-CRF. Patients have to discontinue the study if they experience:

- An AE, including clinically significant abnormal laboratory value(s) which request study termination according to the Investigator's judgement.
- Protocol violation (e.g. prohibited medication, poor compliance with study procedures).
- Patient's request.

Any patient who prematurely terminates participation after having received the dose of the IMP, will be encouraged to undergo the End of Study examinations according to the procedures described under section 8.6.4.1.

NOTE: If study participation is terminated due to an AE the patient has to be followed-up, for details see section Adverse Events Follow-up (§ 8.7.5).

If a patient prematurely terminates the study, data already collected will be used and analysed for the purpose of the study. In regard to biological samples already collected, the patient will be asked if samples already obtained but not yet analysed shall be destroyed or analysed.

8.4 IDENTITY OF THE INVESTIGATIONAL PRODUCT(S)

8.4.1 Description of Investigational Medicinal Product(s)

Test drug:

Dexketoprofen Trometamol/Tramadol Hydrochloride fixed combination of:

Dexketoprofen Trometamol

Chemical name: S-(+)-2-(3-benzoylphenyl) propionate of 1,1,1-tris (hydroxymethyl) methylammonium

Generic name: Dexketoprofen trometamol

Molecular formula: $C_{20}H_{25}NO_6$

Tramadol Hydrochloride

Chemical name: (1RS,2RS)-2-[(Dimethylamino) methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride

Generic name: Tramadol hydrochloride

Molecular formula: $C_{16}H_{25}NO_2$. HCl

Dose for combination:

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

Reference drug:

- TRAM.HCl /paracetamol 75 mg/650 mg, as 2 x [37.5 mg/325 mg] film-coated tablets
- Placebo matching DKP.TRIS/TRAM.HCl 25mg/ 75mg
- Placebo matching active comparator

Dosage form of the treatments: oral film-coated tablets.

Regimen: one single oral dose.

Double dummy technique will be applied to ensure double blind condition of DKP.TRIS/TRAM.HCl 25mg/75mg vs. TRAM.HCl/paracetamol 75mg/650mg vs. placebo administration.

8.4.2 Packaging, labelling, and storage

The packaging and labelling of IMP will be performed by the Sponsor's Pharmaceutical Development Department [redacted] which is also responsible for IMP distribution directly to the study sites or through local depots.

Packaging: The IMP will be provided in treatment boxes (blister cards) to be dispensed at randomisation. The IMP will be packaged in Al-Al blister (primary packaging) which are

permanently fixed in blister cards (secondary packaging) containing 3 film-coated tablets each (as per double-dummy technique).

Labelling: The IMP will be labelled in compliance with the current valid international and corresponding national requirements. The treatment box (blister card) labels will have a peel-off section which has to be attached to the corresponding section in the drug accountability log upon dispensing of the IMP. The peel-off part reports the treatment kit number to identify the treatment as assigned through IxRS. The fixed section of the label will report (blinded) the contents of the treatment box and the instructions how to administer and store the IMP.

Storage: At the study site, the IMP has to be stored at controlled room temperature. The following storage recommendations are in place: "Do not store above 30 °C" and "Store in the original package in order to protect from light". The IMP must be kept in a secure area, out of reach of children and inaccessible to unauthorized individuals.

8.4.3 Rescue medication

Ibuprofen as 400 mg tablets is allowed as RM during the 8-hours assessment post-dose period. Ibuprofen will be provided using the commercial [redacted] RM will be re-packaged in blister cards (1 blister card containing 10 tablets) and re-labelled according to national/international requirements (including at minimum a RM box number and the note "For clinical trial use only") by the Sponsor's Pharmaceutical Development Department. RM will be centrally distributed as described for the IMP (i.e. either by the Sponsor's Pharmaceutical Development Department or by a local depot).

The RM has to be stored in a secure area and below 25 °C, it should be kept out of reach of children and inaccessible to unauthorised individuals.

After randomisation, patients will be provided with the box assigned by IxRS and asked to use it as follows:

At any time during the 8-hour post-dose period, patients will be able to choose to receive RM if they have not achieved adequate pain relief after receiving the study medication; however, they will be encouraged to wait for at least 60 minutes after dosing to allow time for the study treatment effect to take place. Patients will be duly instructed by the Investigator that during the 8-hour post dose period a maximum of 2 tablets of RM will be allowed, each one separated by a minimum interval of 4 hours. Patients will be also instructed to bring back the remaining RM at the End of Study visit.

NOTE: In accordance to the authorised SmPC, the total daily dose of ibuprofen must not exceed 2400 mg.

8.4.4 Drug accountability

Upon receipt of all IMP and RM, study site personnel or designed pharmacist will open the shipment package, verify the contents as stated on the enclosed shipping form, and confirm the receipt through the IxRS.

The IxRS will be used to record the IMP/RM delivery to the study site, the inventory at the site, including dates, quantities, batch/serial numbers, expiry dates. The assignment of the IMP/RM to each patient through the unique code numbers assigned to the IMP/RM (treatment box number) and to the patients (patient number) will be also done through IxRS.

The Investigator will be responsible for documenting the dispensing of the IMP/RM to the patient by entering the treatment box number in the source documents and in the e-CRF from randomisation (day 1).

Patients will be instructed to return used or unused RM box at the End of Study visit.

A RM patient diary will be used by the patient for documentation of RM consumption (as described under 10.1.3) which has to be checked by the Investigator at the End of Study visit in order to document the RM consumption by each patient. The use of RM, as reported in RM patient diary (source document), will be recorded by the Investigator in the e-CRF.

In addition, study sites will maintain drug accountability forms to document the dispensed IMP/RM and returned RM. The peel-off labels of IMP/RM will be stuck on the drug accountability paper forms.

8.4.5 Destruction of surplus medication

At the end of the study, at the latest, all remaining IMP/RM will be reconciled under the responsibility of the Investigator at the site. No later than at the close out visit, the IMP/RM will be returned for destruction to the Sponsor's Pharmaceutical Development Department, or local depots, provided this is not in conflict with any national export legislation. If in any country participating in the study, the return of IMP/RM should require an export licence, the IMP/RM could be locally destroyed there.

8.5 TREATMENTS

8.5.1 Treatment administration - frequency and duration of application

After confirmation of eligibility, patients will be randomly allocated to one of the following 3 arms:

- DKP.TRIS/TRAM.HCl 25mg/75mg as 1 film-coated tablet
- TRAM.HCl/paracetamol 75 mg/650 mg, as 2 x [37.5mg/325mg] film-coated tablets
- Placebo matching DKP.TRIS/TRAM.HCl 25mg/75mg (1 film-coated tablet) and active comparator (2 film-coated tablets)

One single-dose treatment, consisting of three oral film-coated tablets to ensure the double-dummy technique, has to be orally administered together with approximately 150 ml of still/tap water.

8.5.2 Randomisation and blinding

The study will be performed according to a double-blind, double dummy, randomised, parallel-group design.

Patients will be randomised only after confirmation of their eligibility criteria on day 1 within 4 hours after the surgery, to one out of the 3 treatment arms (see section 8.5.1), as per treatment code delivered through IxRS in accordance with the randomisation list. To keep blinded the conditions, placebo tablets matching the DKP.TRIS/TRAM.HCl or TRAM.HCl/paracetamol will be administered as per double-dummy design (fig. 4).

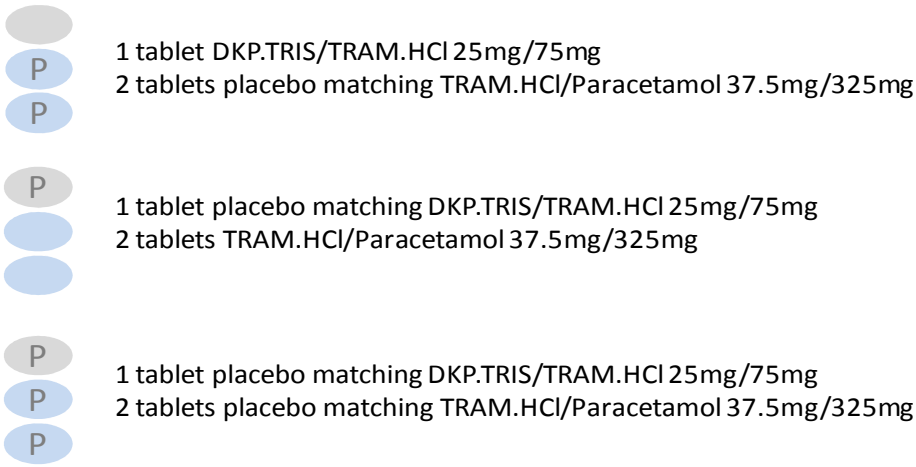


Figure 4. Representation of double dummy design

The Sponsor's delegate will be responsible for generating the randomisation list that will assign the treatment to each patient.

In order to preserve the double-blind conditions of the study, persons who are involved in the preparation or the handling of the randomisation 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 randomisation list will be prepared; one set will be used for programming the IxRS and one set will be provided to Pharmaceutical Development Department of A. Menarini Research & Business Service GmbH, [redacted].

8.5.3 Treatment compliance

Study drugs will be dispensed only under the restricted conditions defined in the present protocol at the study centre and will be administered by the clinical Investigator or under his/her direct supervision.

8.5.4 Concomitant Medication

The use of prior and concomitant medication has to be carefully monitored, since the use of certain drugs represents an exclusion criterion for participation in the study (see § 8.3.2). For this reason, medications taken within 4 weeks of the screening day (prior medication) have to be recorded at screening, while the regular and occasional use of any CM (starting from the screening) has to be recorded at each visit. In order to facilitate recording of medication history, patients will be asked to bring their medication, preferably in their original packaging.

8.5.5 Anaesthetics for Surgery

Surgery will be conducted under local anaesthetic block using 2% lidocaine (with 1:80.000 epinephrine) up to a total volume of 5.4 mL per molar. No sedation is permitted.

Other agents that are not allowed during the surgery include (see also Proibited Medication section):

- Opioids (including meperidine, fentanyl, sufentalin, alfentalin, remifentalin),
- Benzodiazepines (e.g. diazepam),
- All other sedative and hypnotic agents,
- All other local anaesthetics.

8.5.6 Prohibited Medication

- Analgesics, , are prohibited within 12 hours before surgery (5 days prior to the surgery day in case of COX-2 inhibitors) and for 8 hours post-dose [analgesics other than those specified in the protocol (namely study treatments and RM)]. Patients have to agree to take only the defined RM (ibuprofen 400mg) until 8-hour post-dose period.
- Sedatives (e.g. benzodiazepines) and hypnotic agents are prohibited within 12 hours before surgery and for 8 hours post-dose.
- The following medications are prohibited within 48 hours or 5 half-lives (whichever is longer) prior to the start of surgery and for 24 hours post-dose:
    - Anticoagulants, thrombolytic and antiplatelet agents;
    - Corticosteroids;
    - MAO inhibitors - **a minimum of 14 days had to elapse prior to the start of surgery;**
    - Antiepileptics;
    - Antipsychotics;
    - Serotonin reuptake inhibitors and tricyclic antidepressants;
    - Lithium;
    - Metotrexate;
    - Antibacterial Sulphonamides.

8.6 STUDY PROCEDURES AND ASSESSMENTS

8.6.1 Study schedule

The Study Flowchart reported under § 2.2 displays each of the study assessments and procedures together with the scheduled time of occurrence.

Each patient will undergo the study procedures described below, which include at least 3 visits to the study site.

In addition, patients will be asked to record data, during the 8-hour post-dosing period, using the e-Diary provided.

8.6.1.1 Informed consent process

Eligible patients may only be included in the study after they had provided the written informed consent. The informed consent must be obtained before conducting any study-specific procedures (i.e. any of the procedures described in the protocol). The process of obtaining the informed consent shall be documented in the patient source documents.

8.6.1.2 Screening period (within 2 weeks prior to randomisation)

- ***Prior to surgery***

The following procedures/assessments must be completed during the screening period and prior to the surgery day (day 1):

- Collection of demographic data.
- Recording of medical history.
- Recording of prior and concomitant medications (CMs).
- Physical examination including body weight (BW), height (H), and vital signs (VS) (blood pressure [BP], heart rate [HR]).
- Laboratory safety tests (haematology, clinical chemistry, coagulation test and urinalysis).
- Pregnancy test (if applicable).
- Instructions regarding how to complete patient's pain and analgesia assessments, RM intake and [redacted] functionality on e-Diary.
- Recording of adverse events (AEs) occurred since the ICF signature, if any.
- Check of inclusion and exclusion criteria.

- ***Surgery***

The surgical procedure will be performed under local anaesthetic block using 2% lidocaine with 1:80,000 epinephrine up to a total volume of 5.4 ml per molar.

Surgery shall be performed at least one day apart pre-surgery procedures have been completed.

- ***Qualification***

After completion of surgery (last suture), patients will be followed for a period of up to 4 hours and

the following will be performed/assessed:

- Instruct patients to inform the investigator when they experience pain.
- Dispensing of the e-Diary and testing its main functions.
- VS measurement.
- Pregnancy test (if applicable).
- Recording of AEs and changes in CM, if any, since the last assessment.
- Review/Check of inclusion/exclusion criteria.

Patients reporting pain within 4 hours after the end of surgery will be asked to rate their pain intensity (PI) on the e-Diary to assess their eligibility for randomisation. Patients must describe their PI in response to the question: *'How do you rate the intensity of your pain?'* using an 11-point Numerical Rating Scale (NRS) ranging from 0 (no pain) to 10 (worst pain).

NOTES:

1. Only patients experiencing pain of moderate or higher intensity (NRS score ≥4) within the first 4 hours after the end of surgery will be eligible for randomisation.
2. A patient can be screened a maximum of 2 times, provided that he/she was not already randomised and all the inclusion and none of the exclusion criteria are met.
3. Pregnancy test should not be repeated during the qualification period if it was performed the day before as screening procedure.

8.6.1.3 Randomisation, treatment administration and efficacy assessment period (day 1, t_0 - t_{8h})

- ***Randomisation and treatment administration (t_0)***

Patients successfully completing the qualification period will be randomised through IxRS and the corresponding study treatment will be given, as one single oral dose. NRS-PI **immediately prior** to the administration of the study treatment will be recorded as baseline PI (t_{0h}).

A box of RM (ibuprofen 400mg tablets) will be assigned by IxRS and provided to the patients that will be instructed about its usage. A paper diary for RM recording intake will be also given to patients, with the request to return it to the site at the End of Study visit.

- ***8-hour pain and analgesic effect assessment period ($t_0 – t_{8h}$)***

After the study treatment administration, patients will remain under observation at site for two hours (up to t_{2h}).

Pain and analgesia assessment by patients will be performed either at site (from t_{15min} to t_{2h}) and out of the site (from t_{4h} to t_{8h}) by e-Diary recording.

The following items will be recorded by the patients on the e-Diary:

- Pain relief (VRS-PAR): at t_{15min}, t_{30min}, t_{1h}, $t_{1.5h}$, t_{2h}, t_{4h}, t_{6h} and t_{8h}. Patients will be asked to answer the question *'How do you rate your pain relief?'* using a 5-point verbal rating scale

(VRS), where 0 = 'no relief', 1 = 'a little (perceptible) relief', 2 = 'some (meaningful) relief', 3 = 'lot of relief', 4 = 'complete relief'.

- Pain Intensity (NRS-PI): at t_{15min}, t_{30min}, t_{1h}, $t_{1.5h}$, t_{2h}, t_{4h}, t_{6h} and t_{8h}, using the 11-point NRS.
- First intake of RM, if any.
- Onset of analgesia: The *two* [redacted] method will be used to assess the onset of analgesia within the first two hours (from t_0 to t_{2h}): the first stop upon the experience of "first perceptible" PAR (FPPAR) and the second stop when PAR is considered "meaningful" (MPAR).
- Patient Global Evaluation (PGE): at the end of the assessment period (t_{8h}), or immediately before RM intake, if any. Patients 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'.

Occurrence of any AE as spontaneous reporting and changes in CM, if any, will be collected by study staff while the patients are at the site.

NOTE: Patient will be allowed to complete the scheduled assessments on e-Diary within a ±3 minutes time window for t_{15min}, t_{30min}, t_{1h}, $t_{1.5h}$, and t_{2h} time points, and a ±10 minutes time window for t_{4h}, t_{6h} and t_{8h} time points.

Rescue medication

At any time during the 8-hour post-dose period, patients will be allowed to take RM if they have not achieved adequate pain relief after receiving the study medication; however, they will be encouraged to wait for at least 60 minutes after dosing to allow time for the study treatment effect to take place. Patients will be duly instructed by the investigator that during the 8-hour post dose period a maximum of 2 tablets of RM will be allowed, each one separated by a minimum interval of 4 hours. Patients will be also instructed to bring back the remaining RM at the End of Study visit.

NOTE:

After first intake of RM, patients will stop using the e-Diary including the [redacted] functionality. Only the first intake of RM will be recorded on the e-Diary,

Time of each intake of RM, if any, will be recorded by the patients in a paper booklet (RM diary). The Investigator or designee will be responsible for entering diary data into the e-CRF.

8.6.1.4 End of Study visit (6 ± 1 days after randomisation)

- Return of e-Diary, RM diary and unused RM by patients.
- RM accountability.
- Physical examination.
- VS measurement.

- Pregnancy test (if applicable).
- 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 centre to accomplish the procedures from Screening to End of Study. Unscheduled surgical follow-up visits may be requested by the surgeon at an earlier timepoint; however they will not be considered as part of this study.

8.6.2 Surgical Assessment

8.6.2.1 Surgical Trauma Rating Scale

The following surgical trauma rating scale[53] will be used to rate the degree of difficulty of the surgical procedure for each molar tooth removed by the oral surgeon:

Rating	Characteristics
1	Tooth in vertical position, not covered by bone, simple root anatomy without root deviation Operating time less than 5 minutes
2	Mesioangulated tooth in high position, partly impacted in bone, simple root anatomy without root deviation Operating time 5-10 minutes
3	Tooth in mesioangulated or deep horizontal position, fully impacted in bone with or without root deviation Operating time up to 20 minutes
4	Tooth in distoangulated or deep horizontal position, root deviations, close relation to inferior alveolar nerve Operating time usually more than 20 minutes

The corresponding numerical rating for each molar extracted and the total rating will be recorded on the patient's source record and on the e-CRF.

8.6.2.2 Other Surgery Parameters

The following information will be recorded by the Investigator or designee:

- Time of local anaesthetic (i.e. beginning of surgery)
- Time of completion of last suture (i.e. end of surgery)
- Duration of surgery (i.e. time elapsed between the time of local anaesthetic and time of completion of last suture).
- Complications, if any - NOTE: Complications may represent exclusion criteria (see section 8.3.2)
- Number of teeth extracted

8.6.3 Assessments of Efficacy

The analgesic efficacy evaluation will be based on patients' e-Diary scores of PI and PAR at pre-defined intervals during the 8-hour post-dose period; the PGE at the end of the assessment period;

the time to onset of the analgesic effect (limited to the 2-hour post-dose period) and the first use of RM.

8.6.3.1 Pain Intensity Numerical Rating Scale

An 11-point numerical rating scale (ranging from 0 [no pain] to 10 [worst pain], as represented in figure 5) will be used for the subjective assessment of PI[54, 55, 56, 57]. Patients will be asked to select the number that best represents their PI at the time of the assessment.

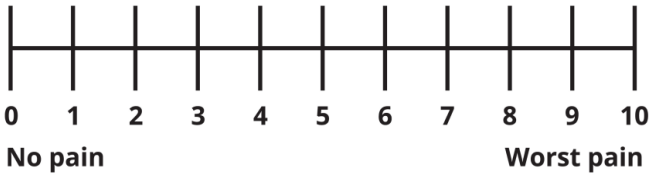


Figure 5. The NRS

NRS-PI will be measured:

- During the qualification period, in order to confirm eligibility, namely *moderate or higher PI (NRS ≥4);*
- immediately prior to the treatment administration (t_{0h}),
- at pre-specified time points during the 8-hour post-dose period, (i.e: at t_{15min}, t_{30min}, t_{1h}, $t_{1.5h}$, t_{2h}, t_{4h}, t_{6h} and t_{8h}).

8.6.3.2 Pain relief Verbal Rating Scale

A 5-point VRS will be used for the 8-hour post-dose PAR subjective assessment [35, 58].

Patients will be asked to answer the question '*How do you rate your pain relief?'* and to select the adjective that best describes the level of pain relief on the e-Diary. The number associated with the adjective chosen by the patient will constitute the experienced pain relief as reported below:

Score	**Pain Relief**
0	No relief
1	A little (perceptible) relief
2	Some (meaningful) relief
3	Lot of relief
4	Complete relief

VRS-PAR will be measured at pre-specified time points during the 8-hour post-dose period, i.e. at t_{15min}, t_{30min}, t_{1h}, $t_{1.5h}$, and t_{2h}, t_{4h}, t_{6h} and t_{8h}.

8.6.3.3 Use of rescue medication

Time of first intake of rescue medication will be recorded on the e-Diary. After this, patients will stop using the e-Diary.

8.6.3.4 Time to onset of analgesia

The [redacted] will be used to assess the onset of analgesia, within the first 2 hours post dose (i.e.: while the patient is still at site).

Patients will be instructed to stop the first [redacted] by pressing the 'first perceptible pain relief' button when the relief from pain is first perceptible (i.e. at the moment they first feel any pain relief whatsoever) (FPPAR) and then to stop the second [redacted] by pressing the 'meaningful pain relief' button when the relief from pain becomes meaningful to them (MPAR).

In case of RM use during the first 2 hours, the patient will be no longer required to use the [redacted] and they will be considered as censored.

FPPAR and MPAR are assessed by [redacted] or the time when the patients report for the first time a pain relief score $\geq$1 and $\geq$2 respectively, whichever happens first.

Time to confirmed FPPAR (time to onset of analgesia) is defined as the time to FPPAR for those patients who achieve meaningful pain relief (MPAR).

8.6.3.5 Patient's Global Evaluation

Patients will be asked to give a subjective overall assessment (PGE) of the study medication by using a 5-point VRS[35, 59].

Patients will be asked to answer the question: *'How would you rate the medication received for your pain?'* and to select the adjective that best rate the study medication that they received for pain relief on the e-Diary. The number associated with the adjective chosen by the patient will constitute the global evaluation score, as reported below:

Score	**PGE**
1	Poor
2	Fair
3	Good
4	Very Good
5	Excellent

The PGE will be recorded at the end of the assessment period (at 8 hours post-dose or whenever the patient uses RM).

8.6.4 Assessment of Safety

Assessment of safety will be based on the evaluation of the following variables:

- Incidence, intensity (severity), seriousness and treatment-causality of TEAEs, i.e. AEs that occurred after study drug intake.
- Frequency of clinically significant changes in:
  - Physical examination
  - VS

  NOTE: for physical examination, the *screening period* values will be used as baseline; for VS, the values collected during the qualification period will be used as baseline.

8.6.4.1 Medical History

A complete medical history will be registered during the Screening period in the subject's source record and reported on the e-CRF, including:

- A thorough review of systems, including any past or current acute conditions (e.g. urinary tract infection), intermittent conditions (e.g. migraine), and chronic conditions (e.g. hypertension).
- Prior surgical procedures.
- Pharmacotherapy and chronic or recent (within 4 weeks of screening) use of any medication (prior medications).
- Allergies or idiosyncrasies to drugs.
- Substance abuse (including alcohol abuse).

Past conditions that no longer affect the subject should not be recorded.

8.6.4.2 Physical Examinations and Vital signs

Physical examination (review of body systems) will be performed during the Screening period and at the End of study visit. Measurement of height (in whole centimetres) and weight (in kilograms to one decimal place) will be performed during the Screening period only.

Vital signs (i.e. BP [systolic and diastolic, mmHg] and HR [beats/min]) will be measured 1) during the screening period, 2) during the qualification period and, 3) at the End of Study visit.

Out of range measures will be repeated at the Investigator's discretion.

The collected data will be registered in the subject's source record and reported on the e-CRF.

8.6.4.3 Clinical Laboratory Evaluation

Blood laboratory safety tests will be performed locally, with blood samples (8ml approximately) collected in fasting conditions during the Screening period. The following parameters will be analysed:

- Haematology: Red blood cell (RBC) count, haematocrit (HCT), haemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), platelet count, white blood cells (WBC) count, and differential WBC count (neutrophil, lymphocyte, monocyte, eosinophil and basophil counts, absolute and %).
- Serum biochemistry: Sodium, potassium, chloride, total calcium, glucose, creatinine, urea, total protein, albumin, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), and creatine phosphokinase (CPK).
- Coagulation test: prothrombin time, partial thromboplastin time (PTT), INR.

Urinalysis will be performed during the Screening period, using Roche Combur-10® dipsticks. The following parameters will be analysed: Specific gravity, pH, leucocytes, nitrite, protein, glucose, ketones, urobilinogen, bilirubin, blood **(**erythrocytes/haemoglobin**)**.

Pregnancy tests (when appropriate) will be performed during the Screening period, during the qualification period and at the End of Study visit, by determination of the urine β human chorionic gonadotropine (ß-HCG), using locally available commercial dipsticks.

Unscheduled re-tests can be performed as required according to the investigator's judgement.

The reference ranges of laboratory parameters described in this study will be submitted by each centre to the sponsor prior to beginning of this study and will be updated as appropriate.

The lab print-outs should be identified with the laboratory requisition number, patient number, patient's age, gender, and site number, as well as with the date and time of sample collection. All results should be reviewed by the Investigator with print-outs being dated and signed by the investigator and stored in the patient's record. Out of range values will be judged by the Investigator as "abnormal clinically significant" or as "abnormal not clinically significant" and stored in the patient's record. Note: abnormal evaluation can be repeated at the Investigator's discretion. Records will be transferred on the e-CRF.

8.6.4.4 Adverse Events/Serious Adverse Events – Definitions

8.6.4.4.1 **Adverse Event (AE)**

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

NOTE: abnormal laboratory findings considered by the Investigator as not clinically significant are not considered AEs.

Treatment-Emergent Adverse Events

AEs will be categorized as Treatment-Emergent Adverse Events (TEAE) or Non-TEAE. If an AE occurs for the first time or if it worsens in terms of seriousness or severity after the first study drug intake it will be classified as TEAE, otherwise it will be classified as non-TEAE.

8.6.4.4.2 **Adverse Drug Reaction (ADR)**

All untoward and unintended responses to an IMP related to any dose administered. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. 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. For causality assessment of AEs, see section 8.6.4.4.6.

8.6.4.4.3 **Intensity (Severity) of an Adverse Event/Adverse Drug Reaction**

It will be assessed based on the following definitions:

- **Mild:** It does not interfere with routine activities;
- **Moderate:** It interferes with routine activities;
- **Severe:** It makes it impossible to perform routine activities.

NOTE: The term '*severe'* is used here to describe the intensity of a specific event. This has to be distinguished from the term *'serious'* (see section 8.6.4.4.4).

8.6.4.4.4 **Serious Adverse Event (SAE)/Serious Adverse Drug Reaction (SADR)**

A Serious Adverse Event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life-threatening;
- requires hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is an 'important medical event' that may jeopardise the patient or may require an intervention to prevent one of the above characteristics/consequences.

These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

NOTE: The term '*hospitalization'* refers here to inpatient admission lasting more than 24 hours.

Any other AE/ADR which is not included in the above definitions will be considered as non serious.

The Investigator has to immediately report all SAEs to the Sponsor, according to the procedures and timelines described in section 8.7.1. The seriousness must be confirmed by the Investigator or a delegated physician.

8.6.4.4.5 **Unexpected Adverse Drug Reactions**

An ADR, the nature or intensity of which is not consistent with the applicable product's safety reference information. Any other ADR which is not included in the above definition will be considered as expected.

In this study, the 'safety reference information' will be the safety section included in the last version of the IMP's Investigator's brochure (IB).

8.6.4.4.6 **Algorithm for Causality Assessment of Adverse Events**

The causality (causal relationship to the study drug) of AEs will be assessed based on the following algorithm:

1. Certainly related: An AE is considered certainly related to a drug when it occurs with a plausible time sequence to the administration of the drug, and which cannot be explained by 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. Probably related: An AE is considered probably related to a drug when it occurs with a reasonable time sequence to the administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information (AE reappearance after drug reintroduction) is not required to fulfil this definition.

3. Possibly related: An AE is considered possibly related to a drug when it occurs with a reasonable time sequence to the administration of the drug, but could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal (dechallenge) may be lacking or unclear.

4. Unlikely related: An AE is considered unlikely related to a drug when the temporal relationship to the drug administration makes a causal relationship improbable (but not impossible) and/or other drugs, chemicals or underlying disease provide plausible explanations.

5. Not related: An AE is considered not related to the use of a drug in case of existence of a clear alternative explanation and/or unreasonable temporal relationship, and/or non plausibility.

6. Unassessable/unclassifiable: The relationship between drug and AE is considered unassessable/unclassifiable when a report, suggesting an adverse reaction, cannot be judged because information is insufficient or contradictory and cannot be supplemented or verified. NOTE: It is the responsibility of the study team to obtain all available information before an AE is definitively classified as *'unassessable / unclassifiable'*.

An AE in which the relationship is ranked 1, 2, 3 or 6 will be considered as an ADR. AEs ranked 4 or 5 will not be considered as ADRs.

8.6.4.5 Monitoring and Recording of Adverse Events

At every study visit patients will be asked a standard question to elicit medically related changes in their well-being. They will be asked if they have been hospitalized, have had any accident, have used any new medication, or have changed concomitant medication regimens (both prescription and over the counter medication).

In addition to the patient observations, AEs may be collected from other sources, e.g. physical examination findings, or other documents that are relevant to patient safety, and recorded in the AE page of the e-CRF.

The Investigator is responsible for the detection and documentation of events meeting the definition of AE, as provided in this protocol (see section 8.6.4.4).

All AEs, whether or not thought to be drug related, must be recorded by the Investigator (or designee) in the source documents and in the appropriate section of the e-CRF throughout the whole study duration, from the Informed Consent signature until the End of Study visit.

In addition any relevant AE Information could be recorded by the investigator in e-CRF only until the last visit of last patient.

8.6.5 Efficacy and Safety Endpoints

8.6.5.1 Primary Endpoint

Total pain relief (TOTPAR), calculated as the weighted sum of the PAR scores (measured according to a 5-point VRS from 0=no relief to 4=complete relief), over 6 hours post-dose ($TOTPAR_6$).

8.6.5.2 Secondary Endpoints

- [redacted]
- [redacted]
- [redacted]
- Percentage of patients achieving at least 50% of maximum TOTPAR over [redacted] 8 hours post-dose.
- [redacted]

- Percentage of patients who achieved at least 30% of PI reduction versus baseline at each pre-specified time point over 8 hours post-dose period.
- [redacted]
- Time to confirmed FPPAR (time to onset of analgesia) - i.e. time to FPPAR if confirmed by experiencing MPAR.
- [redacted]
- PGE of the study medication (measured according to a five-point VRS from 1 = poor to 5 = excellent), at 8 hours post-dose or whenever the patient uses RM.
- [redacted]
- Percentage of patients who required RM within [redacted] 8 hours post-dose.

8.6.5.3 Safety Endpoints

- Incidence, intensity (severity), seriousness and treatment-causality of treatment-emergent AEs (i.e. TEAEs, reported starting from the study medication intake).
- Frequency of clinically significant changes in physical examination and VS, post-dose versus baseline. (NOTE: for physical examination, screening period values will be used as baseline; for VS the values collected during the qualification period will be used as baseline).

8.7 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

8.7.1 Reporting of Serious Adverse Events to the Sponsor

All SAEs, whether or not deemed drug-related or expected, must be recorded in the corresponding section of the e-CRF **within 24 hours** (one calendar day) of awareness. Once the information is saved, a notification e-mail will be automatically generated and sent to the Sponsor's Drug Safety Manager (DSM).

SAE Report Forms in paper support will be provided as a backup, to be used only in case of breakdown of the e-CRF System. Whenever paper SAE Report Forms are used, they must be submitted by fax or e-mail to the Sponsor's DSM, within the same required timeframe.

Sponsor's DSM contact details:

The Sponsor's confirmation of reception of the SAE Report Form must be kept in the patient's records.

The initial SAE entry should include at least the following data:

- A short description of the AE.
- Reason why the event is categorised as serious (seriousness assessment), according to criteria described in section 8.6.4.4.4.
- Causality assessment (according to the algorithm described in section 8.6.4.4.6).
- Study code and patient number (if paper SAE Report Form is used).
- Reporter's name and telephone number for clarifications (if paper SAE Report Form is used).

If not already reported, the full description of the event and outcome must follow within 1 working day.

Any questions arising during the processing and medical review of the SAE will be managed by means of electronic queries (i.e. queries in the e-CRF). In case of breakdown of the e-CRF System, queries will be sent by fax or e-mail.

In case of breakdown of the e-CRF System and the paper SAE Report Form has been sent, the Investigator will be responsible for entering the data in the e-CRF as soon as the system works again.

Any additional information provided by the Investigator as a query reply or as a SAE follow-up will be processed in the same way as the initial SAE report within the same required timeframe.

SAEs occurred after the End of Study visit should be also recorded in e-CRF, if feasible. Otherwise, the paper SAE report form should be completed and sent to the Sponsor's DSM (see section 8.7.5).

8.7.2 Management of Suspected Unexpected Serious Adverse Reactions

For each SAE, assessment of seriousness (according to section 8.6.4.4.4) and causality (according to section 8.6.4.4.6) will be provided by both the reporting Investigator and the Sponsor. The assessment of expectedness (according to section 8.6.4.4.5) will be done by the Sponsor.

NOTE: The causality assessment given by the Investigator will not be downgraded by the Sponsor. If the Sponsor disagrees with the Investigator's causality assessment, the opinions of both, the Investigator and of the Sponsor, will be provided.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are AEs which, cumulatively:

- have a reasonable possibility of causal relationship to the IMP.
- are serious.
- are unexpected.

The Sponsor will ensure that all SUSARs occurred during the study are reported on an expedited basis (7 days or 15 days) to the concerned national CAs and ECs, according to European and/or country-specific legal requirements:

- For fatal or life-threatening SUSARs the Sponsor will report at least the minimum information, as soon as possible, and in any case **no later than 7 days** after being made aware of the case. If the initial report is incomplete, the Sponsor will submit a completed report based on the initial information within an additional 8 days.
- SUSARs which are not fatal and not life-threatening will be reported **within 15 days**.
- The clock for expedited initial reporting (day zero) starts as soon as the information containing the minimum reporting criteria has been received by the Sponsor (or the Sponsor's delegate).

- If significant new information on an already reported case is received by the Sponsor, the clock starts again at day zero (i.e. the date of receipt of new information). This information will be reported as a follow-up report within 15 days.

The Sponsor will also inform all Investigators. Whenever practicable, the information will be aggregated in a 'line listing' of SUSARs in 6 monthly periods.

Events associated with placebo will usually not satisfy the criteria for a SUSAR and therefore for expedited reporting. However, where SUSARs are associated with placebo (e.g. reaction due to an excipient or impurity), the Sponsor will report such cases.

SUSARs identified after the end of the trial will be reported to the CAs by the Sponsor.

8.7.3 Annual Safety Reporting

Once a year throughout the clinical trial, the Sponsor will provide the concerned national CAs and ECs with a safety report (Development Safety Update Report, DSUR), taking into account all new safety information received during the reporting period.

8.7.4 Breaking of the Randomisation Code

Breaking of the treatment code for a specific patient can be requested by the Sponsor's DSM or by the Investigator, by contacting the IxRS.

The Investigator should unblind the treatment allocation in the course of the clinical trial only if this is relevant to the safety of the patient (e.g. in order to offer adequate care for the patient's immediate condition).

If possible, prior to breaking of the code, the Sponsor's DSM and/or the site monitor should be contacted. The Investigator has to document the reason for breaking the code in the IxRS.

As regards the Sponsor, when an event may be a SUSAR, the blind will be broken by the Sponsor's DSM only for that specific patient. The blind will be maintained for persons responsible for the ongoing conduct of the study (such as the management, monitors, Investigators) and those responsible for data analysis and interpretation of study results, such as biometrics personnel.

8.7.5 Serious and Non-serious Adverse Events Follow-up

Non-serious AEs will be recorded until the End of Study visit.

If a patient is withdrawn from the study due to an AE or if a patient has an ongoing SAE at the End of Study visit, the patient has to be followed-up until the event is resolved or until the patient's condition stabilises.

After the last study visit, the Investigator is not requested to actively follow-up the patient (unless ongoing SAEs are present at the End of Study visit). However, if after the end of the trial, the Investigator becomes aware of any SAEs, they should be duly reported to the Sponsor.

If indicated, safety blood tests, urinalysis, and/or any other clinical investigation can be performed to follow-up AEs.

8.8 MANAGEMENT OF POSITIVE PREGNANCY TEST

The Investigator has to inform the Sponsor, within 1 week of awareness, about any unexpected case of pregnancy occurring during the study, monitor the pregnancy until delivery and report whatever outcome to the Sponsor

A specific form ("Pregnancy Exposure Report Form") will be distributed to the sites to be used for this purpose.

The Investigator must immediately (within 24 hours of awareness) report to the Sponsor's DSM any case of pregnancy resulting in an abnormal outcome (miscarriage or newborn with congenital abnormality and/or stillbirth) according to the procedures described for SAEs in section 8.7.1.

9. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.1 DETERMINATION OF SAMPLE SIZE

A sample size of 230 patients per active arm is considered adequate to demonstrate the non inferiority of DKP.TRIS/TRAM.HCl oral fixed combination compared to TRAM.HCl/paracetamol assuming a non-inferiority margin of 20%, a power of 80% and an overall significance level of 2.5 % (1-side). The mean $TOTPAR_6$ for TRAM.HCl/paracetamol is assumed equal to [redacted]

115 patients in placebo arm are sufficient to demostrate the superiority of both TRAM.HCl/paracetamol and DKP.TRIS/TRAM.HCl vs placebo for model sensitivity.

Assuming about 10% of major protocol violators, and 20% of screening failure rate a total of 640 patients need to be randomised and approximately 800 patients are expected to be screened.

9.2 ANALYSIS POPULATIONS

The following analysis populations will be considered:

- Intention-to-treat (ITT) population: All patients randomised.
- Safety population: All patients who have received at least one dose of the study treatment.
- Per protocol (PP) population: All patients of the ITT population who did not experience relevant protocol violations related to efficacy endpoints of primary interest

9.3 STATISTICAL ANALYSIS

9.3.1 Descriptive statistics

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

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

The behavior over time of study variables will be summarized by treatment as follows:

- Continuous variables: descriptive statistics for each time point and for the absolute differences to baseline;
- Discrete variables: descriptive statistics for each time point and shift tables to baseline (where applicable and/or requested).

9.3.2 Primary (efficacy) analysis

The primary efficacy variable will be analyzed on the PP and ITT populations to assess the non-inferiority hypothesis using analysis of covariance (ANCOVA) for testing the differences in treatment efficacy, as quantified by $TOTPAR_6$, between DKP.TRIS/TRAM.HCl and TRAM.HCl/paracetamol.

The ANCOVA model will include terms of treatment and the baseline PI level with one-sided significance level of 2.5%. The following hypothesis will be tested:

$$H_0 : \mu_{TRAM.HCl\ /\ paracetamol} - \mu_{DKP.TRIS\ /\ TRAM.HCl} \geq \delta$$

against

$$H_1 : \mu_{TRAM.HCl\ /\ paracetamol} - \mu_{DKP.TRIS\ /\ TRAM.HCl} < \delta$$

with δ of 20% as non-inferiority limit.

In case the non-inferiority is confirmed, the superiority of DKP.TRIS/TRAM.HCl versus TRAM.HCl/paracetamol will be tested on the ITT population.

Comparison of DKP.TRIS/TRAM.HCl and TRAM.HCl/paracetamol versus placebo will be performed in order to confirm the model sensitivity on the ITT population.

9.3.2.1 Sensitivity analysis

In case non-inferiority is confirmed the primary efficacy endpoint will be also evaluated on the ITT population using other methods of imputation respect to the one described under section 9.3.8 and they will be described in detail in the Statistical Analysis Plan (SAP).

9.3.3 Secondary (efficacy) analysis

$SPID_6$ will be analyzed for non-inferiority with the possibility to switch for superiority analogously to the primary efficacy variable.

All the other secondary efficacy variables will be descriptively analysed. The superiority for DKP.TRIS/TRAM.HCl will be tested on the secondary endpoints when applicable, through an ad hoc inferential analysis, as reported below:

- NRS -PI, SPID, (excluded $SPID_6$), %max SPID, TOTPAR (excluded $TOTPAR_6$), %max TOTPAR (continue variables) will be analyzed analogously to the primary efficacy variable.
- PGE and VRS-PAR (categorical variables) will be analyzed by Wilcoxon rank-sum test.
- Percentage of patients who required rescue medication, and percentage of patients achieving at least 30% of PI reduction, achieving at least 50% max TOTPAR, confirmed FPPAR, MPAR will be tested using a Chi^2-Test.
- Time to use RM, time to FPPAR, confirmed FPPAR and MPAR will be assessed using a Log-rank test.

9.3.4 Exploratory (efficacy) analysis

Exploratory analysis, if any, will be fully described in the SAP.

9.3.5 Subgroup analysis

Subgroup analysis, if any, will be fully described in the SAP.

9.3.6 Safety analysis

The safety analysis will be run on the safety population. Safety analysis will consider AEs, laboratory values, physical examination, VS data. All safety endpoints will be analysed using descriptive statistics.

9.3.6.1 AEs

Adverse Events occurring after treatment administration (TEAEs), will be summarised by primary System Organ Class (SOC) and Preferred Term (PT). For each PT/SOC, the number of TEAEs, the number of patients with TEAEs, and the percentage of patients with TEAE will be given.

TEAEs will be listed by treatment arm, overall and stratified by intensity (mild, moderate, and severe), relationship to the treatment intake (certainly related / probably related / possibly related / unlikely related / not related / unessessable-unclassifiable) and for those leading to study discontinuation.

Serious TEAEs will be analysed analogously as TEAEs.

AEs/SAEs which are not considered TEAE will be included in a separate listing.

All serious TEAEs which have an onset date after the patient's study completion will be included in a separated listing.

Any TEAEs serious or not serious with a relationship to the treatment intake other than "not related" or "unlikely related" will be considered as treatment-related AEs/SAEs (i.e. ADRs/SADRs).

9.3.6.2 Other Safety Variables

Descriptive statistics on vital signs, haematology, serum biochemistry, and urine tests will be presented on the safety population.

Change in vital signs and laboratory values will be also evaluated descriptively.

9.3.7 Interim analysis and stopping rules

No interim analysis is planned for this study.

9.3.8 Data imputations

The method of last observation carried forward (LOCF) will be applied among patients who missed more than one consecutive, otherwise the missing value will be replaced by the mean of the two non missing data collected respectively before and after the missing one. This procedure will be applied to all efficacy outcomes. If PI is missed at t_{0h} the value recorded during qualification procedure will be used as baseline.

After rescue medication intake, PI will return to its baseline (t_{0h}) level and PAR to zero ("no relief") for all subsequent time points (i.e. baseline observation carried forward, BOCF). Different approaches might be applied for sensitivity analysis, as described in section 9.3.2.1

9.4 PROTOCOL VIOLATIONS AND BLIND REVIEW

Categories of protocol violations will be assigned to each potential protocol violation defined before the treatment unblinding and will be integrated in the SAP.

A blind data review meeting (BDRM) 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 violations. Patients who experience relevant protocol violations will be excluded from the PP population (eg: patient did not confirm adequate baseline PI (i.e. ≥4), missing PI and/or PAR assessment in the first 6 hours, study treatment not taken).

After final BDRM take place and the database is considered cleaned, the database will be locked and unblinded.

9.5 STATISTICAL ANALYSIS PLAN

The SAP will be finalised before the unblinding of the study.

The SAP will describe in detail study endpoints and the statistical analyses to be performed, including also additional endpoints and analyses not planned in the protocol.

In case major deviations from the original primary endpoint or from the original primary analyses will occur during the study, these changes will be the subject of a substantial protocol amendment.

No major deviations from the original analysis plan will take place after data unblinding.

Minor deviations (e.g. not involving changes in the primary endpoint and analysis) which might occur during the study will be detailed only in the SAPs.

10. DATA QUALITY MANAGEMENT

10.1 DATA COLLECTION

Data collection activities will be carried out under the responsibility of Sponsor.

Patient data will be collected using various data capture systems described below.

A list of the data capture system versions used and the validation documentation of each version will be maintained. The list and the validation documentation will be provided to the site at the site initiation visit (SIV), filed in the Investigator's file, and will be updated whenever any data capture system version changes.

Patients will be identified by the patient number (patient ID), assigned at the Screening visit.

The patient ID will be a number composed of 8-digits [redacted]

[redacted]

The data will be collected, processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations.

10.1.1 Case Report Forms

Clinical data collected during the study at sites will be recorded in an electronic CRF (e-CRF) using [redacted] which is a validated system. The e-CRF will be developed based on this study protocol under the responsibility of Sponsor that will also perform user acceptance test of the e-CRF in order to ensure the protocol adherence.

The e-CRF will be made available to the study personnel by means of the [redacted] interface which is a validated system. The accounts will be individual and password-protected.

The Investigator or designee (see section 5.5) will be responsible for entering study data into the e-CRF in accordance to the e-CRF Completion Guidelines provided by Sponsor. In order to improve the quality of data collection and cleaning, data shall be entered into the e-CRF as closely as possible to the time when they become available and not later than within 5 working days.

The e-CRF data will never be considered as source data. The definition of the source data can be found in section 10.3.

Investigators will ensure the accuracy, completeness and consistency of data entered signing electronically the e-CRF using the personal password. An audit trail within the system will track all changes made to the data.

10.1.2 IVRS/IWRS

IxR system [redacted], is a validated system used by the site personnel for the registration of IMP, patient screening (including assignment of the patient ID), patient randomisation, kit assignment, patient status change and code break. Site staff will be provided with a personal user name and password to access to IxRS.

Further details will be reported in a separate IxRS user manual specifying the system that will be used (i.e. voice and/or web). The manual will be prepared by [redacted] and provided to site personnel by CRO. Some data (e.g. patient numbers and gender) collected through IxR system could be automatically integrated in e-CRF (the integration process will be detailed in a specific integration document created by Menarini in collaboration with [redacted]).

10.1.3 Patient diary

Efficacy variables (Pain relief [PAR], Pain intensity [PI], first intake of RM, onset of analgesia [FPPAR, MPAR] and Patient's Global Evaluation [PGE]) will be collected with a validated system, using an electronic device (smartphone) provided by the dedicated vendor at site. Patient will complete the questionnaires/recording at site ($t_{0h} - t_{2h}$) and out of the site ($t_{4h} - t_{8h}$) at each time point as per protocol. The patient has to return the electronic device to the site at the end of study visit.

Data will be automatically transferred, as soon as saved by the patient to a central database managed by the dedicated vendor and then automatically integrated in the e-CRF, according to a specific integration document created by Menarini and the dedicated vendor.

Moreover, patients are required to record their use of RM (including the time of each RM intake) for the whole study duration in a paper booklet (RM diary). The patient has to bring the diary to the site at the end of study visit and the completed diary pages have to be checked and collected by the Investigator. The Investigator or designee is responsible for entering RM data from the ad hoc RM diary into the e-CRF.

10.2 CLINICAL DATA MANAGEMENT

Data Management will be carried out under the responsibility of Sponsor.

e-CRF data will be electronically verified through the use of on-line and off-line checks. Discrepancies in the data will be resolved by means of electronic queries. Data will be frozen after source data verification by the monitor, and they will be locked by the data manager when all activities for the trial, including medical revision of the data, are complete and no more entries are expected.

Data from sources other than e-CRF will be provided to the data manager on an agreed scheduled basis. The data manager has the responsibility to reconcile data captured in the e-CRF, with external data sources. Discrepancies found in the reconciliation of the data, will be addressed by means of queries.

A clear overview of all clinical data management activities will be given in the data management plan.

10.3 SOURCE DATA

Source data are defined as all data in original records and certified copies of original records of clinical findings, observations or other activities that are necessary for the reconstruction and evaluation of the trial.

Original documents and data records include, but are not limited to, hospital/patients' medical records, laboratory notes, patients' identification forms, and pharmacy dispensing records, if applicable.

Study sites will also maintain a paper drug accountability forms for the IMP and the RM to document dispensed and returned IMP/RM per patient.

Source data should be held available for perusal by the Sponsor representatives for the study or to other authorised persons such as auditors and inspectors of Regulatory Authorities.

Direct access to source data is defined as the permission to examine, analyse, verify and reproduce any records and reports that are important for evaluation of a clinical trial. Any party allowed to direct access to study source data and documents should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and sponsor proprietary information.

Data should be consistent with the source documents and discrepancies, if any, should be explained in writing.

All the original documentation pertinent to the study procedures must be available for review in each patient's record.

10.4 QUALITY CONTROL/QUALITY ASSURANCE

10.4.1 Study Monitoring

This trial will be monitored in accordance with the ICH Note for Guidance on GCP. Monitoring will be carried out by the appointed CRO. The site monitor will perform visits to the trial sites along the study conduct according to the monitoring plan. Facilities, study drug, storage area, e-CRF, patient's source data, and all other study documentation will be inspected/reviewed by the site monitor for adherence to the protocol and GCP. At each site visit, the monitor will review the e-CRFs for completion and accuracy. Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the e-CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Principal Investigator and site staff.

The Investigator agrees to allow access to all study related materials needed for the proper review of study conduct and to assist the monitor during the monitoring visits and the data cleaning process.

All monitoring activities will be described in detail in the study-specific monitoring plan.

10.4.2 Quality Assurance

Independent study audit(s) and/or inspection(s) may take place at any time during or after the trial. The independent audit/inspection can be carried by the Quality Assurance (QA) Department of the CRO, the independent QA Department [redacted] or a Competent Authority. At all times, the confidentiality of subject related documents will be maintained.

11. PREMATURE TERMINATION OF THE WHOLE STUDY

The whole trial may be discontinued at the discretion of the Sponsor in the event of any of the following:

- New information leading to unfavourable risk-benefit judgement of the investigational products due to:
  - Occurrence of significantly previously unknown AEs or unexpectedly high intensity or incidence of known AEs
  - New evidence of unfavourable safety or efficacy findings (from clinical or non-clinical examinations, e.g. toxicology)
- The Sponsors decision that continuation of the trial is unjustifiable for medical or ethical reasons
- Discontinuation of development of the IMP

Competent Authorities and IECs will be informed about the discontinuation of the trial in accordance with applicable regulations.

12.END OF CLINICAL TRIAL AND ARCHIVING

The clinical trial will end with the collection and analysis of study data and the issue of the clinical study report. All essential documents will be finally archived by the Sponsor according to the relevant SOP.

12.1 ARCHIVING OF ELECTRONIC DOCUMENTATION/DATE

Duplicate electronic media such CDs/DVDs (one for routine access and one for back-up) containing the patient data in PDF format (e.g. e-CRFs, e-Diary) for each site will be prepared by the Sponsor or a delegate for archiving purposes. The electronic media, of a (not re-printable type) will be appropriately labelled recording the files/data included. The files should contain at least the e-data copy clearly reporting the study code and the e-CRF/e-Diary version used; for e-CRF data also the electronic signature and the associated audit trails have to be included.

Patient data relevant for each site will be distributed to the Investigator, who has to confirm the receipt of the material, verify whether the provided electronic media represent a copy of data generated during the study and sign a dedicate form provided by the Sponsor, the signed form has to be collected and archived at the Sponsor.

Two copies of the same electronic media prepared for the sites or cumulative electronic media with the same content will be archived by the Sponsor. In addition the Sponsor is responsible to create 2 electronic media (one for routine access and one for back-up) containing an integrated SAS database with all study data (eg: e-CRF, e-Diary, IxRS), following appropriate refreshment procedures.

Investigators and Sponsor will be also responsible to refresh their electronic media approximately every 7 years to ensure long term archiving of files/data.

13. REFERENCES

[1]WMA Declaration of Helsinki- Ethical Principles for Medical Research involving Human Subjects. 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

[2]Committee for Proprietary Medicinal Products (CPMP). Note for guidance on clinical investigation of medicinal products for treatment of nociceptive pain (CPMP/EWP/612/00); November 2002.

[redacted]

[redacted]

[redacted]

[redacted]