Public Assessment Report
Scientific discussion

Enanplus 75 mg/25 mg and Takudex 75 mg/25 mg Film-coated Tablets

(TramadoI hydrochloride/ Dexketoprofen)
Registration number in Spain:80.925, 80.802

EU-procedure number:
ES/H/0317/001/DC
ES/H/0318/001/DC

Applicant: Laboratorios Menarini, S.A. and Guidotti Farma S.L.

This module reflects the scientific discussion for the approval of Enanplus 75 mg/25 mg and Takudex 75 mg/25 mg Film-coated Tablets. The procedure finalised on 07/01/2016. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This decentralised procedure application concerns a fixed dose combination of tramadol hydrochloride and dexketoprofen trometamol under Enanplus 75 mg/25 mg film-coated tablets and Takudex 75 mg/25 mg film-coated tablets trade names.

The legal basis of the application is Article 10b of Directive 2001/83/EC, as amended, i.e. fixed combination application.

With Spain as the Reference Member State in this Decentralized Procedure, Laboratorios Menarini, S.A. and Guidotti Farma S.L applied for Marketing Authorisations for Enanplus 75 mg/25 mg film-coated tabletsand Takudex 75 mg/25 mg film-coated tablets in the following Concerned Member States:

- ES/H/0317/001/DC: AT, BE, BG, CY, CZ, DE, DK, EE, EL, FI, FR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK and UK.
- ES/H/0318/001/DC: IT.

The initially intended indication was the treatment of moderate to severe acute pain in adults.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States recommended the approval for Enanplus 75 mg/25 mg film-coated tablets and Takudex 75 mg/25 mg film-coated tablets.

II. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

ACTIVE SUBSTANCES

Tramadol hydrochloride

Tramadol hydrochloride is a known active substance described in Ph. Eur. A Ph. Eur. Certificate of Suitability (CEP) has been submitted to support the quality of the active ingredient.
The CEP includes a re-test period of three years for the drug substance if stored in the described container.

Dexketoprofen trometamol

There is no Ph. Eur. monograph for dexketoprofen trometamol. The ASMF procedure has been used for this drug substance.
Description of the manufacturing process is sufficiently detailed. Elucidation and

characterization of the drug substance are adequate. Proposal on impurities to control and their qualification is also adequate.
Specification for drug substance is considered acceptable, analytical methods are correctly described and their validation is performed according to ICH. Analytical results of a number of batches are sufficient to confirm drug product consistency and uniformity and to support the proposed specifications.
Proposed reference material is satisfactory and is correctly certified.
Dexketoprofen trometamol is packaged into double non toxic polythene bags individually sealed with a plastic crimped strip and then put into fiber drums. The cover of the fiber drum is sealed by a metallic ring.
Stability studies have been performed according to ICH/CPMP guidelines. The studies guarantee the proposed retest period (5 years) and storage conditions (protected from light in a polyethylene bag inside a plastic drum or opaque cardboard box).

FINISHED PRODUCT

Description of the product

The combination of the two active pharmaceutical ingredients dexketoprofen trometamol and tramadol hydrochloride has been developed as film-coated tablets.
The qualitative composition of the film-coated tablets is as follows:
Tablet Core:

- Microcrystalline cellulose
- Maize Starch, pregelatinised
- Croscarmellose sodium
- Sodium stearyl fumarate
- Silica colloidal, anhydrous

Film-coating:

- Polyvinyl alcohol
- Titanium dioxide
- Macrogol/PEG 3350
- Talc

Tablets are provided in blister packs, in three alternative materials:
- PA/Aluminum/PVC //Aluminum blister
- PVC/PE/PVDC//Aluminum blister
- PVC/PVDC//Aluminum blister

Pharmaceutical development

Pharmaceutical development has been described. Knowledge of the product and manufactured process is gained from a risk assessment and design of experiments. Manufacturing development of the clinical batches is presented.

Manufacture of the product and process controls

The manufacturing process is sufficiently described and the process controls are appropriate, considering the nature of the product and the manufacturing method.
The commercial batch size is defined.
The dossier includes sufficient validation data to guarantee that the manufacturing process is controlled and to ensure batch to batch reproducibility and compliance with product specifications.

Excipients

The information provided is adequate. The specifications for the different excipients are justified by their official adoption in the relevant Ph. Eur. monograph or by an in-house monograph (for the non-compendial excipient).

Product specification

The specifications proposed for the film-coated tablets are adequate. The limits proposed for the different parameters have been adequately justified.
The analytical methods have been properly described and validated.

Container closure system

Tablets are provided in blister packs, in three alternative materials:
- PA/Aluminum/PVC //Aluminum blister
- PVC/PE/PVDC//Aluminum blister
- PVC/PVDC//Aluminum blister

The components of the container closure systems comply with the specifications established.

Stability of the product

The stability studies have been performed following the ICH guidelines. The stability data support the proposed shelf-life and storage conditions.

II-2 Non-clinical aspects

Both dexketoprofen and tramadol hydrochloride are well known active substances. Dexketoprofen trometamol is an analgesic, anti-inflammatory and antipyretic drug. It is the tromethamine salt of S-(+)-2-(3-benzoylphenyl) propionic acid, belonging to the non-steroidal anti-inflammatory drugs (NSAIDs) group. The mechanism of action of NSAIDs is described via the inhibition of cyclooxygenase pathway. Both isoforms of cyclooxygenase (COX-1 and COX-2) are inhibited by dexketoprofen. In the case of tramadol, it is a centrally acting synthetic opioid analgesic, acting as a non-selective, partial agonist of μ-, δ- and κ-opioid receptors.

For the present application of Tramadol/ Dexketoprofen, and taking into account that it is a fixed combination of two well-known active substances, the non-clinical information has been mainly obtained from the published literature. The dossier describes, mainly using data and results of published literature, the pharmacodynamics, pharmacokinetics and general toxicity profile of dexketoprofen and tramadol. The Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005) has been taken into account for this Assessment Report.

The Applicant has conducted an Environmental Risk Assessment (ERA) for both active substances, as requested by Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00). The report includes a Phase I Estimation of Exposure and a Phase II Environmental Fate and Effects analysis. However, the information related to tramadol is considered inconclusive. At the end of the procedure, the Applicant committed to perform additional tests related to the environmental fate and effect analysis for tramadol.

Pharmacology

The two components of the combination, dexketoprofen and tramadol have pharmacological actions that have been examined in experimental animals and in humans over many years. As a consequence, a vast amount of data has been accumulated on their actions and the mechanisms by which they achieve their beneficial analgesic effects. Pharmacological aspects related to potential interactions between dexketoprofen and tramadol have been updated and included in the provided documentation. Similarly, and given that tramadol is a well-known partial agonist of opioid receptors, the information related to dependence and abuse potential of tramadol has been also incorporated to the non-clinical sections of the dossier.

According to the Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005), when the fixed combination under development includes compounds for which there is sufficiently documented human experience of their individual and combined use, safety studies in animals are in general not required (CPMP/EWP/240/95). Both drug substances are routinely used in the clinical practice. Therefore, except for the (lack of) effects on hERG currents and on cardiovascular parameters in conscious dogs, no new non-clinical pharmacological investigations have been conducted in support of this Application.

Pharmacokinetics

Plasma levels of dexketoprofen and tramadol were measured in a cardiovascular safety dog study as proof of exposure and toxicokinetics analyses were performed in repeated (13 weeks) oral doses in the rat study. In both studies, the results indicate that pharmacokinetic parameters of dexketoprofen and tramadol do not appear to be affected from the concomitant administration of the two drugs. Given the considerable amount of data published related to the pharmacokinetics (absorption, distribution, metabolism and excretion) of dexketoprofen and tramadol, the performance of additional studies is considered not required.

Toxicology

Most of the toxicological information has been obtained from studies available in the literature. The two components have been extensively studied in a variety of preclinical species (mice, rat, dog and monkey) and additionally through the therapeutic use in humans over many years.

In accordance with Guideline on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (ICH M3), both compounds are considered as late stage entities (Phase III or post marketing medicinal products). Consequently, no combination studies are recommended unless there is a significant concern. In this regard, 28- and 90-day combination drug toxicity studies were conducted, in which no increased or additional toxicity was reported during the co-administration of both compounds. Similarly, toxicokinetic parameters (AUCs and Cmax) do not differ from the single administration of each product.

Environmental Risk Assessment (ERA)

An Environmental Risk Assessment report has been submitted. In the ERA phase I, calculation of the Predicted Environmental Concentration (PEC) and action limits has been determined. As the $PEC_{surfacewater}$ values for both components are all above the action limit of 0.01 ε g/L further risk assessment in Phase II of the procedure required (0.375 and 1.125 µg/L for dexketoprofen

and tramadol, respectively). An extensive ERA Phase II has been conducted for the two active substances. In the case of dexketoprofen, risk assessment is considered completed. For the tramadol active substance, some studies are missing and consequently required. The Applicant committed to submit the results of these studies.

II.3 Clinical aspects

INTRODUCTION

The mechanism of action of non-steroidal anti-inflammatory drugs like dexketoprofen trometamol is related to the reduction of prostaglandin synthesis by the inhibition of cyclooxygenase pathway.

Specifically, there is an inhibition of the transformation of arachidonic acid into cyclic endoperoxides, PGG2 and PGH2, which produce prostaglandins PGE1, PGE2, PGF2Ŭ and PGD2 and also prostacyclin PGI2 and thromboxanes (TxA2 and TxB2). Furthermore, the inhibition of the synthesis of prostaglandins could affect other inflammation mediators such as kinins, causing an indirect action, which would be additional to the direct action.

Dexketoprofen has been demonstrated to be an inhibitor for COX-1 and COX-2 activities in experimental animals and humans.

Tramadol hydrochloride is a non-selective, partial agonist of ε-, ŭ- and ə-opioid receptors with a higher affinity for ε-receptors. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to ε-opioid receptors. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound. Tramadol has also been shown to inhibit reuptake of norepinephrine and serotonin in vitro, as other analgesic opioids. These mechanisms may contribute independently to the overall analgesic profile of tramadol.

In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

Tramadol/dexketoprofen is a new fixed combination tablet containing the well-established active ingredients tramadol hydrochloride and dexketoprofen trometamol that have not been used in combination before.

In support of this application, the following studies have been submitted:

- A phase I safety and pharmacokinetics (PK) study (DEX-TRA-PK) that aimed investigating the potential for drug-drug interactions between of single agents as well as their tolerability when administered concomitantly as a single oral dose to healthy subjects.

- DEX-TRA-02 was a double-blind, randomised, placebo and active controlled, parallel group, phase II dose-finding study; it was performed in patients with acute pain of moderate-severe intensity after impacted third mandibular molar extraction. The aims of the study were to evaluate the analgesic efficacy and safety of dexketoprofen trometamol (12.5mg and 25mg) and tramadol hydrochloride (37.5mg and 75mg)

combined at different ratios (4 different combinations), and administered as single components in comparison to placebo.

– DEX-TRA-04 and DEX-TRA-05 were the two phase III pivotal studies performed in order to confirm the superiority of the fixed-dose combination tramadol hydrochloride 75mg + dexketoprofen 25mg over the single components in the treatment of moderate to severe acute pain. The analgesic effect was evaluated in two validated models of visceral (mixed) and somatic pain of moderate to severe intensity, namely abdominal hysterectomy (DEX-TRA-04) and total hip arthroplasty (DEX-TRA-05). Both studies were designed to test the efficacy of a single dose, the sustained effect of multiple-doses, as well as safety and tolerability of the combination over 3 or 5 days, respectively. In both studies, one of the single components (tramadol hydrochloride 100mg) was given at a higher dose than in the fixed-dose combination (75mg), as recommended during the AEMPS SA to avoid the risk of underdosing patients. Placebo was included during the single-dose phase to validate the pain model, while the multiple-dose phase included only the fixed-dose combination and related mono-components.

PHARMACOKINETICS

In the clinical development program two tramadol/dexketoprofen film-coated tablets formulations were used, Formulation I and Formulation II.

Dexketoprofen trometamol is a class IIa drug whose C_{max} cannot be predicted by means of *in vitro* dissolution studies. In contrast, dexketoprofen AUC is not expected to differ between formulations. Sooner or later the whole dose is absorbed in the intestine and the rate of absorption does not affect the first-pass effect.

In the case of tramadol, AUC and C_{max} are expected to be similar based on the very rapid dissolution characteristics of the product and the use of conventional excipients because it is considered a class I drug, although the Applicant has not formally shown that it can be classified as a class I drug.

Any small difference in the C_{max} of formulation I with respect to formulation II is not considered critical since this formulation was employed only in the phase II dose-finding study.

As tramadol/dexketoprofen is a new fixed combination tablet containing the well-established active ingredients tramadol hydrochloride and dexketoprofen trometamol that have not been used in combination before. The efficacy and safety of the applied formulation has been investigated in two phase III studies. Therefore, in this application it is not essential to demonstrate bioequivalence between the free combination of the recognized reference formulations of the individual mono-components and the marketing formulation (fixed combination), because the efficacy and safety is not based on those of the concomitant administration of individual reference products. However, it is necessary to describe the biopharmaceutical performance of the applied product by means of a comparative bioavailability study with the individual reference products administered concomitantly.

The Applicant has submitted a phase I safety and pharmacokinetics (PK) study (DEX-TRA-PK), that aimed at investigating the potential drug-drug interactions between the single products.

Regarding tramadol, historical data from another applicant was used for the inter-study comparison and a formal analysis was not conducted because the raw data was not available. PK

values seemed to be similar. In addition tramadol is a drug with no critical absorption (Class I drug).

In conclusion, the new pharmacokinetic data of TRAM/DKP 75mg/25mg film coated tablet which has been tested in a Bioequivalence trial and the available PK data for the DKP 25 mg reference tablet (study DEX-TRA-PK) and TRAM 75 mg reference tablet provides an adequate characterization of the TRAM/DKP 75mg/25mg film-coated tablet *per se* and in comparison to the PK data of the single components.

The rate and the extent of absorption (C_{max} and AUC) of tramadol and dexketoprofen administered as single agents were not modified by concomitant administration of an extemporaneous combination of the two drugs.

In addition, the lack of pharmacokinetic interactions in the distribution, metabolism and excretion has been addressed with literature data.

Based on the literature data submitted by the Applicant it can be concluded that drug-drug interactions are very unlikely.

PHARMACODYNAMICS

Mechanism of action

Dexketoprofen trometamol is the tromethamine salt of S-(+)-2-(3-benzoylphenyl)propionic acid, an analgesic, anti-inflammatory and antipyretic drug, which belongs to the non-steroidal anti-inflammatory group of drugs (M01AE).

The mechanism of action of non-steroidal antiinflammatory drugs is related to the reduction of prostaglandin synthesis by the inhibition of cyclooxygenase pathway. Specifically, there is an inhibition of the transformation of arachidonic acid into cyclic endoperoxides, PGG2 and PGH2, which produce prostaglandins PGE1, PGE2, PGF2Ŭand PGD2 and also prostacyclin PGI2 and thromboxanes (TxA2 and TxB2). Furthermore, the inhibition of the synthesis of prostaglandins could affect other inflammation mediators such as kinins, causing an indirect action which would be additional to the direct action.

Dexketoprofen has been demonstrated to be an inhibitor for COX-1 and COX-2 activities in experimental animals and humans.

Tramadol hydrochloride is a centrally acting synthetic opioid analgesic. It is a non-selective, partial agonist of ε-, ŭ- and ə-opioid receptors with a higher affinity for ε-receptors. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound.

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin in vitro, as do some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol.

Tramadol has an antitussive action. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also gastrointestinal motility is less affected.

Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine

Pharmacodynamic effects

Preclinical studies have shown a synergistic interaction between the active ingredients observed during both acute and chronic inflammation models and suggest that lower doses of each active ingredient allow to obtain effective analgesia. Please refer to preclinical data.

No further pharmacodynamics data are considered necessary.

CLINICAL EFFICACY

The clinical documentation on efficacy of the fixed-dose combination of TRAM.HCl and DKP.TRIS includes three randomised, controlled trials in different models of moderate to severe acute pain as proposed by the Guideline on the clinical development of medicinal products intended for the treatment of pain (EMA/CHMP/970057/2011).

The main characteristics of the studies are summarised in Table below:

Summary of the Efficacy Studies with DKP.TRIS + TRAM.HCl.

Study Identifier	Objective(s)	Indication	No of Subjects (ITT Pop)	DKP/TRAM doses*	Control drug(s)	Duration of Treatment
DEX-TRA-02	Efficacy (dose-finding) and Safety	Moderate to Severe Acute Pain (impacted third molar extraction)	611	12.5/37.5 25/37.5 12.5/75 25/75 tablets	DKP12.5 tablets DKP25 tablets TRAM37.5 tablets TRAM75 tablets IBU tablets PBO tablets	single dose
DEX-TRA-04	Efficacy and Safety	Moderate to Severe Acute Pain (Post-operative visceral pain: Abdominal hysterectomy)	606	25/75 tablets	DKP25 tablets TRAM100 capsules PBO tablets PBO capsules	3 days t.i.d.
DEX-TRA-05	Efficacy and Safety	Moderate to Severe Acute Pain (Post-operative somatic pain Total Hip Arthroplasty)	641	25/75 tablets	DKP25 tablets TRAM100 capsules PBO tablets PBO capsules	5 days t.i.d.
Total			**1858**			

*DKP/TRAM (DKP.TRIS + TRAM.HCl) doses expressed as amount of dexketoprofen in mg / amount of tramadol hydrochloride in mg.

Abbreviations: DKP: Dexketoprofen Trometamol; IBU: Ibuprofen; ITT Pop: Intention To Treat Population; PBO: Placebo; t.i.d.: three times a day; TRAM: Tramadol Hydrochloride;

Three different accepted acute pain models were chosen for the phase II (impacted third molar extraction) and III trials (post-operative visceral pain: abdominal hysterectomy and post-operative somatic pain: total hip arthrosplasty). Visceral and somatic pain models are covered and various short-term treatment durations are included (3 days for abdominal hysterectomy and 5 days for total hip arthroplasty). This medicinal product is not intended for long term use and the treatment must be limited to the symptomatic period and in any case for a maximum of 5

days. Although the study has been conducted up to 5 days, efficacy endpoints collected data were during the first 48 hours.

Dose response study- *DEX-TRA 02 Study(Moderate to Severe Dental Pain)*

DEX-TRA-02 study was a multicentre, randomised, double-blind, double-dummy, parallel, placebo and active-controlled, single-dose, dose-finding phase II study aimed at evaluating the analgesic efficacy and safety of DKP.TRIS and TRAM.HCl given as 4 different combinations (DKP12.5/TRAM37.5; DKP25/TRAM37.5, DKP12.5/TRAM75; DKP25/TRAM75), and as single components (DKP12.5; DKP25; TRAM37.5; TRAM75) in comparison to placebo, on moderate to severe acute pain following impacted third molar tooth extraction. The active control ibuprofen 400 mg arm was included in order to validate the pain model.

The study design encompassed a total of 10 balanced treatment arms, with the 4 combinations of DKP.TRIS + TRAM.HCl, the 4 corresponding single treatments, placebo and ibuprofen, as described below:

DEX-TRA-02 Study Arms and Treatments

Arm	Treatment
DKP12.5/TRAM37.5	DKP.TRIS 12.5mg + TRAM.HCl 37.5mg
DKP25/TRAM37.5	DKP.TRIS 25mg + TRAM.HCl 37.5mg
DKP12.5/TRAM75	DKP.TRIS 12.5mg + TRAM.HCl 75mg
DKP25/TRAM75	DKP.TRIS 25mg + TRAM.HCl 75mg
DKP12.5	DKP.TRIS 12.5 mg
DKP25	DKP.TRIS 25mg
TRAM37.5	TRAM.HCl 37.5
TRAM75	TRAM.HCl 75mg
IBU	Ibuprofen 400mg
PBO	Placebo
Abbreviations: DKP, DKP.TRIS: Dexketoprofen Trometamol; IBU: Ibuprofen; PBO: Placebo; TRAM, TRAM.HCl: Tramadol Hydrochloride.	

Male or female patients between 18 to 70 years scheduled for outpatient surgical extraction - under local anaesthesia- of third mandibular molar teeth, with at least one of which is fully or partially impacted in the mandible requiring bone manipulation and who experienced moderate to severe pain (Visual Analogue Scale VAS Ó 40mm ï ranging from 0 to 100mmï and Verbal Rating Scale, VRS Ó 2 ï ranging from 0 to 3ï) after the extraction were randomised to receive 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.

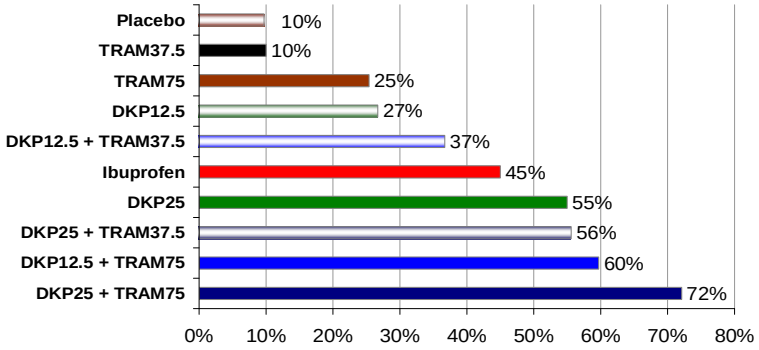
The analgesic efficacy evaluation was based on patient assessments of pain intensity (PI; measured according to a 4-point VRS), pain relief (PAR; measured according to a 5-point VRS) at regular intervals over the 24-hour post-dosing period, patient global evaluation (PGE; measured according to a 5-point VRS) at the end of the assessment period and the use of RM.

Baseline observation carried forward (BOCF) was applied in case of RM use (i.e., PI returned to its baseline level and PAR to zero for all subsequent time points).

A total of 611 patients (247 males and 364 females), mean age 26.9 years (range 18 to 64 years), were randomised and received the study treatment, therefore constituting the safety population. The efficacy analysis was run on the ITT population, which included 606 patients (with balanced allocation into the 10 treatment arms). All treatment groups were comparable in terms of demographic and baseline characteristics.

The primary endpoint of the study, the percentage of patients showing response (achievement of at least 50% max TOTPAR) over 6 hours post-dose, was significantly superior to placebo for all DKP/TRAM combinations and also for DKP25 ($p<0.0001$ for each comparison, except $p=0.0009$ for DKP12.5/TRAM37.5). The highest percentage of responders was achieved in the DKP25/TRAM75 group (72% versus 10% in the placebo group). The active control (ibuprofen 400mg) showed statistical superiority versus placebo ($p<0.0001$), thus validating the pain model. The analysis run on the PP population confirmed the primary efficacy results. The secondary efficacy variables overall supported the results of the primary efficacy endpoint.

DEX-TRA-02 Primary Endpoint: Percentage of Responders (at least 50% max TOTPAR) over 6 hours



Main studies - *DEX-TRA-04 Study (Post-operative moderate to severe Visceral: Pain Abdominal Hysterectomy) and DEX-TRA-05 Study (Moderate to Severe Acute Pain after Elective Unilateral Total Hip Arthroplasty*)

Clinical trials design

DEX-TRA 04 and DEX-TRA 05 wereboth multicenter, randomized, double-blind, double-dummy, parallel-group, placebo and active controlled studies to evaluate the analgesic efficacy, safety and tolerability of the oral TRAM.HCL 75 mg + DKP.TRIS 25 mg fixed combination on moderate to severe pain following abdominal hysterectomy (DEX-TRA-04) or elective unilateral total hip arthroplasty (DEX-TRA-05) in comparison to DKP.TRIS (25 mg) and TRAM.HCL (100 mg) given in monotherapy over a single-dose phase and a multiple-dose phase. During the single-dose phase, single agents were compared to placebo in order to validate the pain model.

Table-Clinical trials design

Study identifier	**DEX-TRA-04**; EudraCT No: 2012-004545-32 **DEX-TRA-05**; EudraCT No: 2012-004548-31		
Treatments groups All study treatments were administered every 8 hours over a period of 3 days (DEX-TRA-04, only one dose on Day 3) or 5 days (DEX-TRA-05).	Single-dose phase		Multiple-dose phase
	DKP.TRIS + TRAM.HCL		DKP.TRIS + TRAM.HCL
	DKP.TRIS		DKP.TRIS
	TRAM.HCL		TRAM.HCL
	Placebo		DKP.TRIS + TRAM.HCL
	Placebo		DKP.TRIS
	Placebo		TRAM.HCL
Mean endpoints and definitions	Primary endpoint	SPID8	Mean Sum of Pain Intensity Differences (SPID) at Rest over 8 hours after the first dose (SPID8) Superiority of DKP.TRIS + TRAM.HCL vs DKP.TRIS and vs TRAM.HCL (Co-primary)
	Secondary endpoint	PI	Mean Pain intensity (PI-VAS: 100-point VAS) scores at rest and on movement over single and multiple-dose phase.
	Secondary endpoint	Pain relief	Mean pain relief (PAR) (verbal rating scale (VRS) 5-scores), over single and multiple-dose phase.
	Secondary endpoint	Rescue medication	Time to first use of rescue medication. Use of RM overall and over 24 and 48 hours of the multiple-dose phase.

The design of these phase III studies (DEX-TRA 04 and DEX-TRA 05) were overall in line with the Spanish National Scientific advice dated on 06/06/2012. Most of the recommendations were taken into account and were incorporated to the clinical trial.

The dose selected for the phase III studies (DKP.TRIS 25mg + TRAM.HCl 75mg) is considered adequate as well as the 8 hours posological scheme.

Considering that the approved posology for tramadol varies country by country, TRAM.HCl could be given at 75mg every 6 hours or at 100 mg for an 8 hour posological scheme. However,

paying attention to the fact that that the primary endpoint is intended to be tested at 8 hours and that TRAM.HCl 75 mg could be under-dosed if is given every 8 hours (instead of every 6 hours), the dose of 100 mg every 8 hours is considered adequate although is higher than the combination.

The use of placebo group was highly recommended during all the phases of the study not only during single-dose phase. In any case, the study design seems adequate to fully characterise the analgesic effect of DKP.TRIS + TRAM.HCl in the most sensitive single-dose model as well as in the closer clinical setting of the multiple doses model.

Use of metamizole as rescue medication is considered acceptable. As well as it is the use of paracetamol in multiple-dose phases as antipyretic. Their use should be properly registered.

Although inclusion criteria stated that ñPI was measured only after cessation of postoperative analgesic care (1 hour or 2 hours were to elapse in case of i.v. or i.m. administration, respectively)ò, median time elapsed from discontinuation of postoperative analgesic care to randomization observed during both studies was about 5-8 hours, which is compatible with the expected duration of short-acting opioids analgesic effect. In any case, this data could have influenced the single dose phase but not the multiple dose phase.

The primary efficacy endpoint (mean sum of pain intensity differences at rest, over 8 hours after the first dose, SPID8) is acceptable although its interpretation is not intuitive. Mean PI-VAS scores at rest over 8 hours after the first dose (included as secondary efficacy variable) is more intuitive. For this variable, differences close to 10 mm point out of 100 mm on the VAS scale are *a priori* considered as the minimum clinically relevant difference.

To sum up, the design is considered overall acceptable.

Main Efficacy Results from Phase III trials

Single dose phase

Primary endpoint SPID8

Regarding the primary efficacy variable (SPID8) in the ITT population, it can be concluded that differences between the combination and monocomponents are statistically significant (>35 mm*h). SPID, although is an acceptable endpoint, is not intuitive and easy to be interpreted.

DEX-TRA-04 - Mean Sum of Pain Intensity Differences (SPID) at Rest over 8 hours after the first dose (SPID8)

Population						
Treatment A	Treatment B	Point Estimate (SE) (Treatment A)	Point Estimate (SE) (Treatment B)	Estimated Treatment Difference (SE) (Treatment A – Treatment B)	95% CI	p-value
ITT Population						
DKP+TRAM	DKP	237.8 (11.20)	180.3 (11.24)	57.5 (15.76)	26.5 to 88.4	<0.001
DKP+TRAM	TRAM	237.8 (11.20)	152.9 (11.28)	84.8 (15.79)	53.8 to 115.8	<0.001
DKP	PBO	180.3 (11.24)	112.2 (11.22)	68.1 (15.76)	37.2 to 99.1	<0.001
TRAM	PBO	152.9 (11.28)	112.2 (11.22)	40.7 (15.79)	9.7 to 71.7	0.010

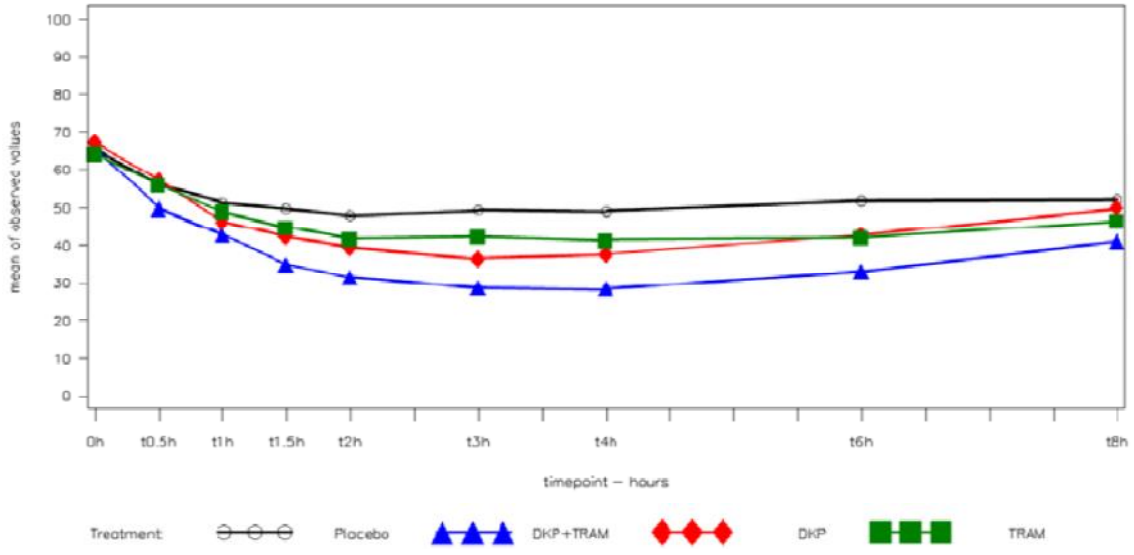
DEX-TRA-05 - Mean Sum of Pain Intensity Differences (SPID) at Rest over 8 hours after the first dose (SPID8)

Population						
Treatment A	Treatment B	Point Estimate (SE) (Treatment A)	Point Estimate (SE) (Treatment B)	Estimated Treatment Difference (SE) (Treatment A – Treatment B)	95% CI	p-value
ITT Population						
DKP+TRAM	DKP	247.5 (11.92)	208.1 (11.88)	39.4 (16.83)	6.4 - 72.5	0.019
DKP+TRAM	TRAM	247.5 (11.92)	205.0 (11.88)	42.5 (16.83)	9.5 - 75.6	0.012
DKP	PBO	208.1 (11.88)	151.5 (11.88)	56.6 (16.81)	23.6 - 89.6	<0.001
TRAM	PBO	205.0 (11.88)	151.5 (11.88)	53.5 (16.81)	20.5 - 86.5	0.002

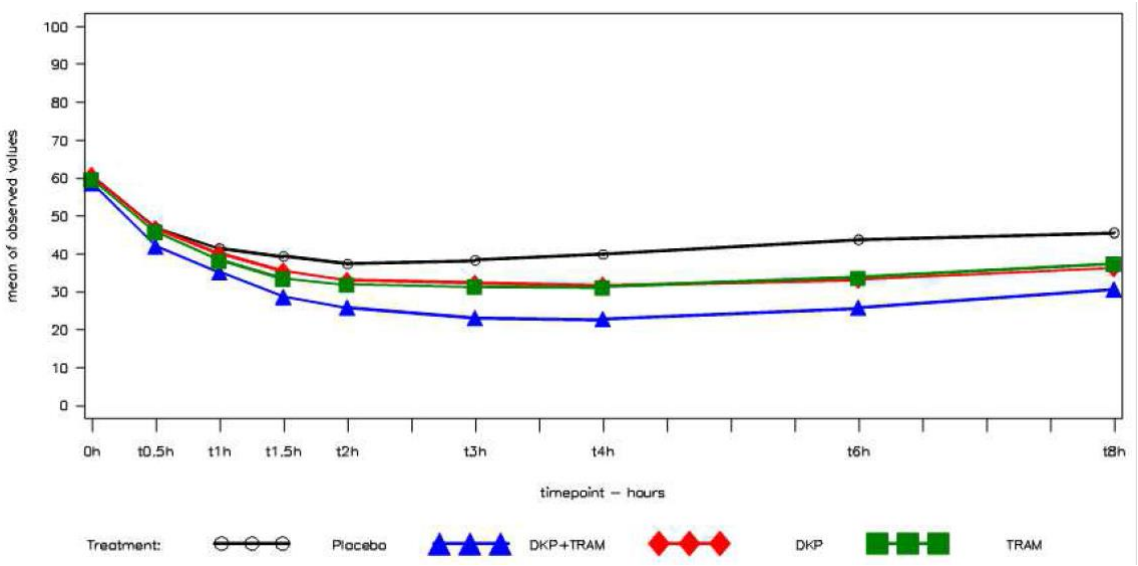
Secondary endpoint ï PI-VAS over 8 hours

Regarding the secondary endpoints (mean Pain Intensity-VAS scores at rest, over 8 hours after first dose), results can be considered more or less in line with SPID8 endpoint. In PI-VAS, clinical meaningful differences are usually established around 10 mm out of 100 mm VAS. However, as the dose of tramadol tested in the monocomponent arm was 100 mg, higher than 75mg used in the combination arm, the assessor considers that 7 mm could be roughly considered acceptable.

DEX-TRA-04: Observed PI-VAS at Rest for the Single-dose Phase by Treatment (ITT Population)



DEX-TRA-05: Observed PI-VAS at Rest for the Single-dose Phase by Treatment (ITT Population)


mean of observed values
100
90
80
70
60
50
40
30
20
10
0
0h
t0.5h
t1h
t1.5h
t2h
t3h
t4h
t6h
t8h
timepoint -- hours
Treatment:
Placebo
DKP+TRAM
DKP
TRAM

DEX-TRA-04: Statistical Analysis (ANCOVA) of PI-VAS at Rest for the Single dose Phase by Treatment and Time Point (ITT population).

Time point		Estimated Treatment Difference (SE) (Treat. A – Treat. B)	95% CI	p-value
Treatment A	**Treatment B**			
Single-dose t0h				
DKP/TRAM 25/75	DKP 25	-1.5 (1.25)	-3.9 to 1.0	0.237
DKP/TRAM 25/75	TRAM 100	1.6 (1.25)	-0.8 to 4.1	0.195
DKP 25	PBO	2.0 (1.25)	-0.5 to 4.4	0.114
TRAM 100	PBO	-1.1 (1.25)	-3.6 to 1.3	0.370
Single-dose t0.5h				
DKP/TRAM 25/75	DKP 25	-7.1 (2.23)	-11.5 to -2.7	0.002
DKP/TRAM 25/75	TRAM 100	-5.8 (2.23)	-10.2 to -1.4	0.009
DKP 25	PBO	1.4 (2.23)	-3.0 to 5.8	0.526
TRAM 100	PBO	0.1 (2.23)	-4.2 to 4.5	0.949
Single-dose t1h				
DKP/TRAM 25/75	DKP 25	-3.7 (2.44)	-8.5 to 1.1	0.130
DKP/TRAM 25/75	TRAM 100	-6.2 (2.44)	-11.0 to -1.4	0.012
DKP 25	PBO	-4.4 (2.44)	-9.2 to 0.3	0.069
TRAM 100	PBO	-2.0 (2.44)	-6.8 to 2.8	0.420
Single-dose t1.5h				
DKP/TRAM 25/75	DKP 25	-7.1 (2.55)	-12.1 to -2.1	0.005
DKP/TRAM 25/75	TRAM 100	-9.8 (2.55)	-14.8 to -4.8	<0.001
DKP 25	PBO	-7.3 (2.55)	-12.3 to -2.3	0.004
TRAM 100	PBO	-4.6 (2.55)	-9.6 to 0.4	0.070
Single-dose t2h				
DKP/TRAM 25/75	DKP 25	-7.9 (2.59)	-13.0 to -2.8	0.002
DKP/TRAM 25/75	TRAM 100	-10.0 (2.60)	-15.1 to -4.9	<0.001
DKP 25	PBO	-8.3 (2.59)	-13.4 to -3.2	0.002
TRAM 100	PBO	-6.1 (2.60)	-11.2 to -1.0	0.019
Single-dose t3h				
DKP/TRAM 25/75	DKP 25	-7.9 (2.56)	-12.9 to -2.8	0.002
DKP/TRAM 25/75	TRAM 100	-13.5 (2.57)	-18.5 to -8.5	<0.001
DKP 25	PBO	-12.6 (2.56)	-17.6 to -7.5	<0.001
TRAM 100	PBO	-7.0 (2.57)	-12.0 to -1.9	0.007
Single-dose t4h				
DKP/TRAM 25/75	DKP 25	-9.4 (2.61)	-14.5 to -4.3	<0.001
DKP/TRAM 25/75	TRAM 100	-12.9 (2.61)	-18.1 to -7.8	<0.001
DKP 25	PBO	-11.0 (2.61)	-16.2 to -5.9	<0.001
TRAM 100	PBO	-7.5 (2.61)	-12.6 to -2.4	0.004
Single-dose t6h				
DKP/TRAM 25/75	DKP 25	-9.5 (2.59)	-14.6 to -4.4	<0.001
DKP/TRAM 25/75	TRAM 100	-8.6 (2.59)	-13.7 to -3.5	<0.001
DKP 25	PBO	-8.7 (2.59)	-13.8 to -3.6	<0.001
TRAM 100	PBO	-9.6 (2.59)	-14.7 to -4.5	<0.001
Single-dose t8h				
DKP/TRAM 25/75	DKP 25	-8.9 (2.64)	-14.1 to -3.8	<0.001
DKP/TRAM 25/75	TRAM 100	-5.4 (2.64)	-10.5 to -0.2	0.043
DKP 25	PBO	-1.7 (2.64)	-6.9 to 3.5	0.517
TRAM 100	PBO	-5.3 (2.64)	-10.5 to -0.1	0.045

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; DKP: Dexketoprofen Trometamol; ITT: Intent-to-Treat; PBO: Placebo; PI-VAS: Pain Intensity-Visual Analogue Scale; SE: Standard Error; TRAM: Tramadol Hydrochloride

DEX-TRA-05: Statistical Analysis (ANCOVA) of PI-VAS at Rest for the Single dose Phase by Treatment and Time Point (ITT population)

Time point Treatment A	Treatment B	Estimated Treatment Difference (SE) (Treat. A – Treat. B)	95% CI	p-value
Single-dose t0h				
DKP/TRAM 25/75	DKP 25	-1.9 (1.30)	-4.5 – 0.7	0.143
DKP/TRAM 25/75	TRAM 100	-1.0 (1.30)	-3.6 – 1.6	0.441
DKP 25	PBO	0.1 (1.30)	-2.5 – 2.7	0.935
TRAM 100	PBO	-0.8 (1.30)	-3.4 – 1.8	0.539
Single-dose t0.5h				
DKP/TRAM 25/75	DKP 25	-4.7 (2.05)	-8.7 – -0.7	0.022
DKP/TRAM 25/75	TRAM 100	-3.7 (2.05)	-7.7 – 0.4	0.074
DKP 25	PBO	0.1 (2.05)	-3.9 – 4.1	0.965
TRAM 100	PBO	-1.0 (2.05)	-5.0 – 3.1	0.643
Single-dose t1h				
DKP/TRAM 25/75	DKP 25	-5.0 (2.28)	-9.5 – -0.6	0.028
DKP/TRAM 25/75	TRAM 100	-3.1 (2.28)	-7.6 – 1.3	0.167
DKP 25	PBO	-1.0 (2.27)	-5.5 – 3.4	0.647
TRAM 100	PBO	-2.9 (2.27)	-7.4 – 1.5	0.200
Single-dose t1.5h				
DKP/TRAM 25/75	DKP 25	-7.0 (2.37)	-11.7 – -2.3	0.003
DKP/TRAM 25/75	TRAM 100	-4.8 (2.37)	-9.5 - -0.2	0.043
DKP 25	PBO	-3.4 (2.37)	-8.1 – 1.2	0.147
TRAM 100	PBO	-5.6 (2.37)	-10.3 – -1.0	0.018
Single-dose t2h				
DKP/TRAM 25/75	DKP 25	-7.3 (2.41)	-12.0 – -2.6	0.003
DKP/TRAM 25/75	TRAM 100	-6.1 (2.41)	-10.9 – -1.4	0.011
DKP 25	PBO	-4.0 (2.41)	-8.7 – 0.8	0.102
TRAM 100	PBO	-5.1 (2.41)	-9.8 – -0.4	0.034
Single-dose t3h				
DKP/TRAM 25/75	DKP 25	-9.2 (2.52)	-14.2 – -4.3	<0.001
DKP/TRAM 25/75	TRAM 100	-8.3 (2.52)	-13.2 – -3.3	0.001
DKP 25	PBO	-5.7 (2.52)	-10.7 – -0.8	0.023
TRAM 100	PBO	-6.7 (2.52)	-11.6 – -1.7	0.008
Single-dose t4h				
DKP/TRAM 25/75	DKP 25	-8.9 (2.57)	-13.9 – -3.8	<0.001
DKP/TRAM 25/75	TRAM 100	-8.5 (2.57)	-13.5 – -3.4	0.001
DKP 25	PBO	-7.9 (2.56)	-13.0 – -2.9	0.002
TRAM 100	PBO	-8.3 (2.56)	-13.3 – -3.3	0.001
Single-dose t6h				
DKP/TRAM 25/75	DKP 25	-7.4 (2.51)	-12.4 – -2.5	0.003
DKP/TRAM 25/75	TRAM 100	-8.0 (2.51)	-12.9 – -3.1	0.002
DKP 25	PBO	-10.2 (2.51)	-15.2 – -5.3	<0.001
TRAM 100	PBO	-9.7 (2.51)	-14.6 – -4.7	<0.001
Single-dose t8h				
DKP/TRAM 25/75	DKP 25	-5.4 (2.61)	-10.5 – -0.3	0.040
DKP/TRAM 25/75	TRAM 100	-6.8 (2.61)	-11.9 – -1.7	0.009
DKP 25	PBO	-9.2 (2.60)	-14.4 – -4.1	<0.001
TRAM 100	PBO	-7.8 (2.60)	-12.9 – -2.7	0.003

Abbreviations: ANCOVA: Analysis of Covariance; CI: Confidence Interval; DKP: Dexketoprofen Trometamol; ITT: Intent-to-Treat; PBO: Placebo; PI-VAS: Pain Intensity-Visual Analogue Scale; SE: Standard Error; TRAM: Tramadol Hydrochloride

In both studies, differences are statistically significant from 1.5h to 8 h. In DEX-TRA-04 results are clinically relevant from 1.5h to 6 h and in DEX-TRA-05 from 3h to 6h.

Multiple dose phases

It might be considered acceptable that the primary endpoint could be focused on the single dose. However, the secondary endpoints are expected to support the main outcome. In this regard, efficacy in the multiple-dose periods must be demonstrated as well.

Secondary endpoints: SPID 24 hours and SPID 48 hours

DEX-TRA-04 - Mean Sum of Pain Intensity Differences (SPID) at Rest over 24 and 48 hours after the first dose (SPID24 and SPID48)

$SPID_{24}$						
DKP+TRAM	DKP	983.2 (31.60)	808.0 (31.69)	175.3 (44.32)	88.2 to 262.3	<0.001
DKP+TRAM	TRAM	983.2 (31.60)	835.0 (31.85)	148.2 (44.43)	61.0 to 235.5	<0.001
$SPID_{48}$						
DKP+TRAM	DKP	2197.1 (59.62)	1887.2 (59.80)	309. 9 (83.63)	145.6 to 474.1	<0.001
DKP+TRAM	TRAM	2197.1 (59.62)	1954.8 (60.10)	242.2 (83.84)	77.6 to 406.9	0.004

DEX-TRA-05 - Mean Sum of Pain Intensity Differences (SPID) at Rest over 24 and 48 hours after the first dose (SPID24 and SPID48)

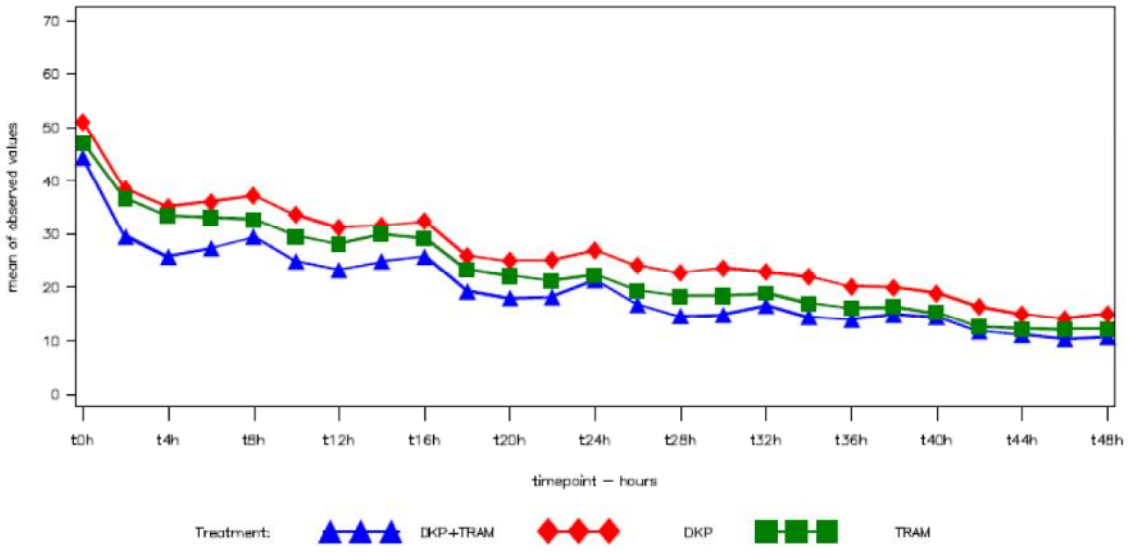
$SPID_{24}$						
DKP+TRAM	DKP	928.9 (33.95)	752.2 (33.95)	176.7 (48.01)	82.4-271.0	< 0.001
DKP+TRAM	TRAM	928.9 (33.95)	826.5 (33.95)	102.4 (48.01)	8.1-196.7	0.033
$SPID_{48}$						
DKP+TRAM	DKP	1948.6 (65.13)	1674.4 (65.13)	274.2 (92.11)	93.3-455.0	0.003
DKP+TRAM	TRAM	1948.6 (65.13)	1770.5 (65.13)	178.1 (92.11)	-2.8-359.0	0.054

The secondary endpoints SPID24 and SPID48 are statistically significant, seeming also clinical relevant (24h: 35mm*h x 3=105mm*h and 48h: 35mm*h x 6=210mm*h) in DEX-TRA-04. However, these endpoints are not judged as clinical relevant for the comparison of combination versus monocomponent tramadol in DEX-TRA-05. When it comes to finding out the possible causes behind that fact, one of them could be the use rescue medication.

Secondary endpoint PI-VAS over 24 hours and PI-VAS over 48 hours

Regarding PI-VAS, although the combination gets low pain intensity levels in all time-points, the differences of the combination versus monocomponents do not seem clinically relevant. Few time-points for multiple dose are over 7mm for the combination versus both monocomponents (DEX-TRA-04: t2h and t4h and DEX-TRA-05: t2h, t4h, t6h y t22h).

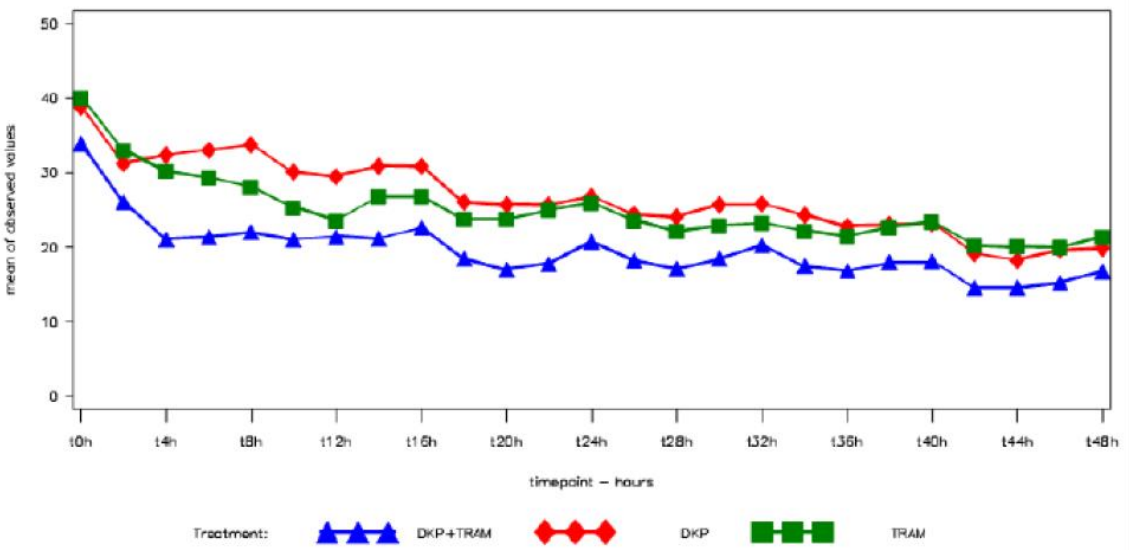
DEX-TRA-04: Observed PI-VAS at Rest for the Multiple-dose Phase by Treatment (ITT Population)



DEX-TRA-04: Statistical Analysis (ANCOVA) of PI-VAS at Rest over 48 hours for the Multiple-dose Phase Mixed Model Repeated Measures (MMRM) by Treatment (ITT Population)

Time point		Estimated Treatment Difference (SE) (Treat. A – Treat. B)	95% CI	p-value
Treatment A	Treatment B			
ITT Population				
DKP/TRAM 25/75	DKP 25	4.5 (1.50)	-7.5 to -1.6	0.003
DKP/TRAM 25/75	TRAM 100	-1.9 (1.50)	-4.9 to 1.0	0.202

DEX-TRA-05: Observed PI-VAS at Rest for the Multiple-dose Phase by Treatment (ITT Population)



DEX-TRA-05: Statistical Analysis (ANCOVA) of PI-VAS at Rest over 48 hours for the Multiple-dose Phase Mixed Model Repeated Measures (MMRM) by Treatment (ITT Population)

Time point Treatment A	Treatment B	Estimated Treatment Difference (SE) (Treat. A – Treat. B)	95% CI	p-value
ITT Population				
DKP/TRAM 25/75	DKP 25	-5.1 (1.69)	-8.4 to -1.8	0.002
DKP/TRAM 25/75	TRAM 100	-4.7 (1.69)	-8.0 to -1.4	0.005

Sensitivity analyses on impact of rescue medication (multiple doses phase)

As rescue medication seemed to have impact on results, sensitivity analyses on impact of rescue medication were requested.

Use of rescue medication (metamizol).

	At least 1	DKP/TRAM 25/75	DKP 25mg	TRAM 100mg	Placebo	Overall
DEX-TRA-04	**Single dose**	12/152 **(7.9%)**	28/151 **(18.5%)**	32/150 **(21.3%)**	52/153 **(34.0%)**	124/606 **(20.5%)**
	Multiple dose	14/203 **(6.9%)**	25/202 **(12.4%)**	24/201 **(11.9%)**	-	63/606 **(10.4%)**
DEX-TRA-05	**Single dose**	15/159 **(9.4%)**	21/161 **(13.0%)**	25/160 **(15.6%)**	48/161 **(29.8%)**	109/641 **(17.0%)**
	Multiple dose	21/213 **(9.9%)**	53/214 **(24.8%)**	42/214 **(19.6%)**	-	116/641 **(18.1%)**

The impact of the rescue medication was assessed by 'censoring' and considering as 'missing' the PI-VAS reported by patients after RM intake.

With this approach, the following results were observed in SPID and Pain Intensity over 24 and 48 hours.

Secondary endpoints: SPID 24 hours and SPID 48 hours

Impact of RM on theTime-course of mean (s.e.) SPID by treatment and study

		DEX-TRAM-04				DEX-TRAM-05			
SPID24				Difference	P value			Difference	P value
DKT+ TRAM	**DKT**	925.6 (34.51)	720.3 (39.25)	205.3	**<0.0001**	875.8 (36.91)	684.3 (41.33)	191.5	**0.0003**
DKT+ TRAM	**TRAM**	925.6 (34.51)	766.2 (38.34)	159.4	**0.0023**	875.8 (36.91)	699.6 (38.42)	176.2	**0.0011**
SPID48									
DKT+ TRAM	**DKT**	2037.7 (72.60)	1658.4 (81.93)	379.3	**0.0004**	1800.8 (73.45)	1417.6 (83.96)	383.2	**0.0003**
DKT+ TRAM	**TRAM**	2037.7 (72.60)	1763.3 (80.46)	274.4	**0.0099**	1800.8 (73.45)	1436.9 (78.19)	363.9	**0.0008**

* SPID24 and SPID48 of the multiple dose refer to the period 8-32 hours and 8-56 hours post randomisation, being the multiple-dose start at 8 hours post the first dose intake

After taking into account the impact of RM, endpoints SPID24 and SPID48 were statistically significant for all comparison in both studies.

Without the impact of RM, endpoints SPID24 and SPID48 were statistically significant for all comparison in both studies except for the SPID 48 comparison of combination versus monocomponent tramadol in DEX-TRA-05. As consequence, rescue medication seems to be a plausible cause to justify the lack of clinical relevance on DEX-TRA-05 study.

Secondary endpoints: PI-VAS over 24 hours and PI-VAS over 48 hours

The results in DEX-TRA-05 showed a relevant impact of rescue medication in this clinical trial. In this study the differences between the combination and mono-components are over 8 points (VAS), which is considered clinical relevant and statistically significant. However, the impact of rescue medication in DEX-TRA-04 is limited, clinical relevance in PI-VAS over 24 and 48 hours versus tramadol is not reached even after considering the rescue medication impact.

PI-VAS over 24 hours of the Multiple-dose Phase with and without RM impact

			Without RM impact			With RM impact		
Study	**Treat. A**	**Treat. B**	**Estimated Difference (SE) Treat A– Treat B**	**95% CI**	**p-value**	**Estimated Difference (SE) Treat A– Treat B**	**95% CI**	**p-value**
DEX-TRA-04	DKP/TRAM	DKP	-6.6 (1.70)	-10.0 to -3.3	**<0.0001**	-8.4(2.17)	-12.6 to -4.1	**0.0001**
	DKP/TRAM	TRAM	-3.4 (1.70)	-6.8 to -0.1	**0.0435**	-4.6(2.17)	-8.9 to -0.4	**0.0329**
DEX-TRA-05	DKP/TRAM	DKP	-7.3 (1.80)	-10.8 to -3.8	**<0.0001**	-8.7(2.12)	-12.8 to -4.5	**<0.0001**
	DKP/TRAM	TRAM	-5.5 (1.80)	-9.0 to -2.0	**0.0024**	-8.4(2.12)	-12.6 to -4.3	**<0.0001**

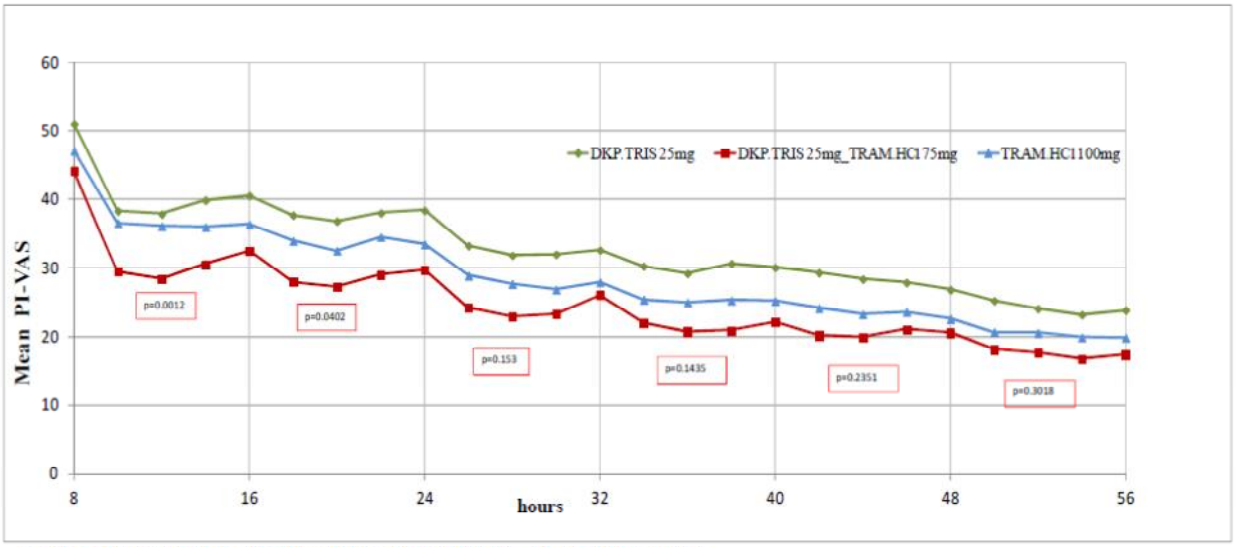
PI-VAS over 48 hours of the Multiple-dose Phase with and without RM impact

			Without RM impact			With RM impact		
Study	**Treat. A**	**Treat. B**	**Estimated Difference (SE) Treat A– Treat B**	**95% CI**	**p-value**	**Estimated Difference (SE) Treat A– Treat B**	**95% CI**	**p-value**
DEX-TRA-04	DKP/TRAM	DKP	-4.5 (1.50)	-7.5 to -1.6	**0.003**	-7.8 (2.17)	-12.0 to -3.5	**0.0004**
	DKP/TRAM	TRAM	-1.9 (1.50)	-4.9 to 1.0	**0.202**	-4.6 (2.17)	-8.8 to -0.3	**0.0362**
DEX-TRA-05	DKP/TRAM	DKP	-5.1 (1.69)	-8.4 to -1.8	**0.002**	-8.7 (2.11)	-12.9 to -4.6	**<0.0001**
	DKP/TRAM	TRAM	-4.7 (1.69)	-8.0 to -1.4	**0.005**	-8.5 (2.11)	-12.7 to -4.4	**<0.0001**

Figure 5a DEX-TRA-04 Time course of mean PI over 48 hours of the Multiple-dose Phase and analysed by dose interval

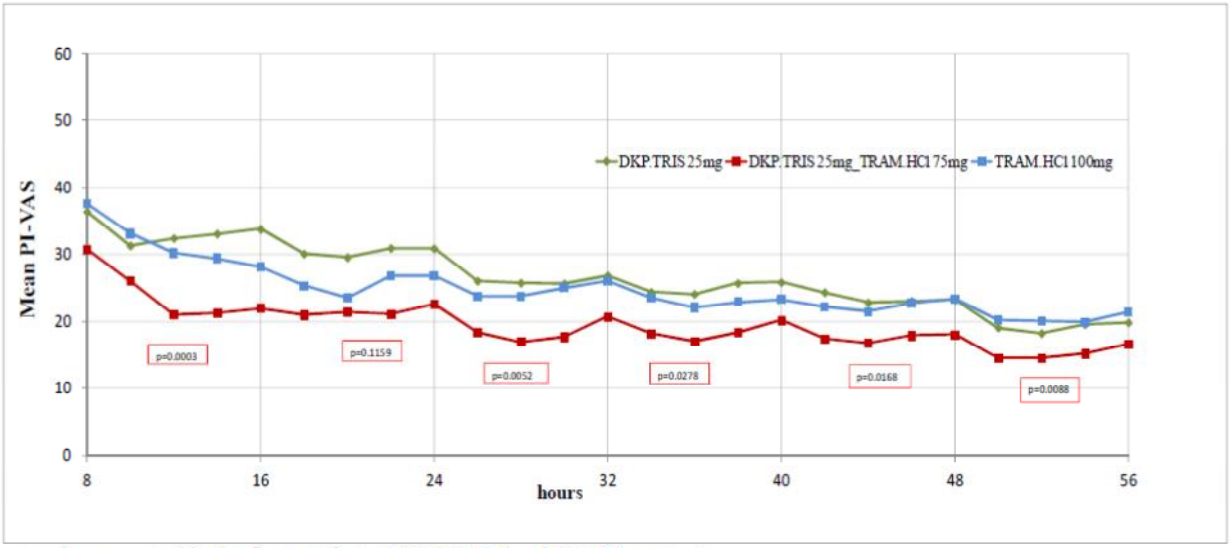
p values reported in the figure refer to DKP/TRAM and TRAM contrast

Figure 5b DEX-TRA-04 Impact of RM on Time course of mean PI over 48 hours of the Multiple-dose Phase and analysed by dose interval



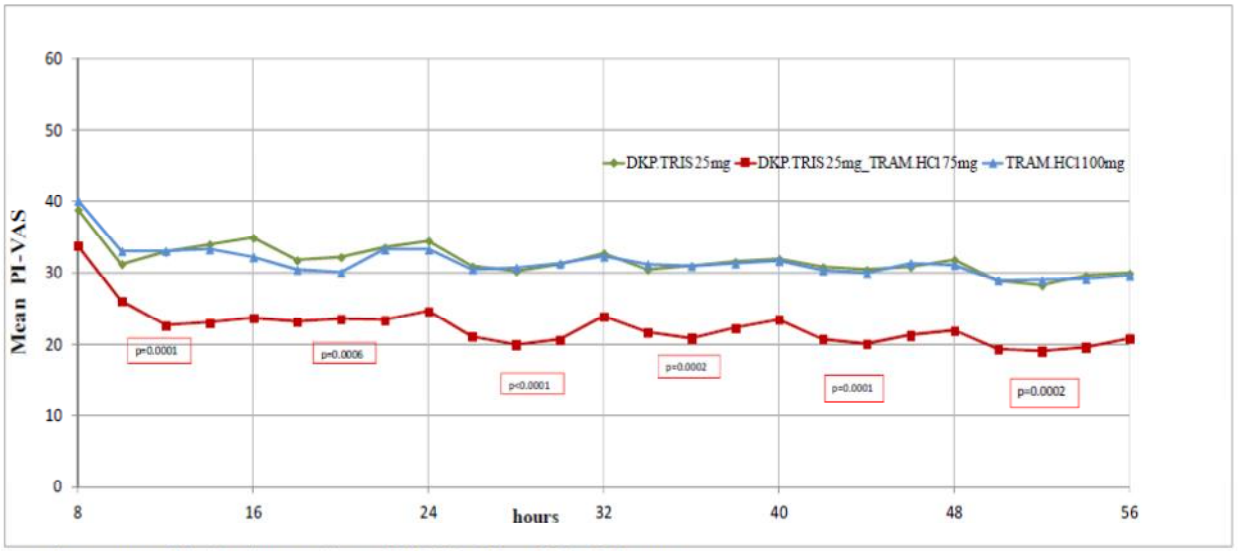
p values reported in the figure refer to DKP/TRAM and TRAM contrast

Figure 6a DEX-TRA-05 Time course of mean PI over 48 hours of the Multiple-dose Phase and analysed by dose interval



p values reported in the figure refer to DKP/TRAM and TRAM contrast

Figure 6b DEXTRA-05 Impact of RM on Time course of mean PI over 48 hours of the Multiple-dose Phase and analysed by dose interval



p values reported in the figure refer to DKP/TRAM and TRAM contrast

<u>Sensitive analysis with ITT population excluding subset of patients who have received placebo during the single dose phase.</u>

Additional analyses were submitted where the ITT population was modified excluding the subset of patients who have received placebo during the single dose phase. It should be noted that patients from placebo arm in single dose phase were randomized to treatment arms in multiple-dose phase. The randomization of patients from placebo arm, which have different baseline pain intensity in multiple dose phase, could have impact on results. Additionally, this

approach would be a more actual scenario to the current clinical practice. Therefore, the applicantós proposal where the ITT population was modified excluding the subset of patients who have received placebo during the single dose phase (n= 453 for study DEXTRA-04 and n= 480 for study DEX-TRA-05) is considered acceptable as sensitive analysis.

Taking into account the above mentioned approach and the impact of rescue medication the superiority in efficacy of the combination versus monocomponents could be considered demonstrated over 56 hours on both pain models (somatic and visceral) this is supported by primary endpoint SPID8 (as mentioned on Day 180 assessment report) and secondary endpoints based on pain intensity (VAS).

DEX-TRA-04 ï PI-VAS over single dose (0-8 hours) and multiple dose phases (8-56 hours)

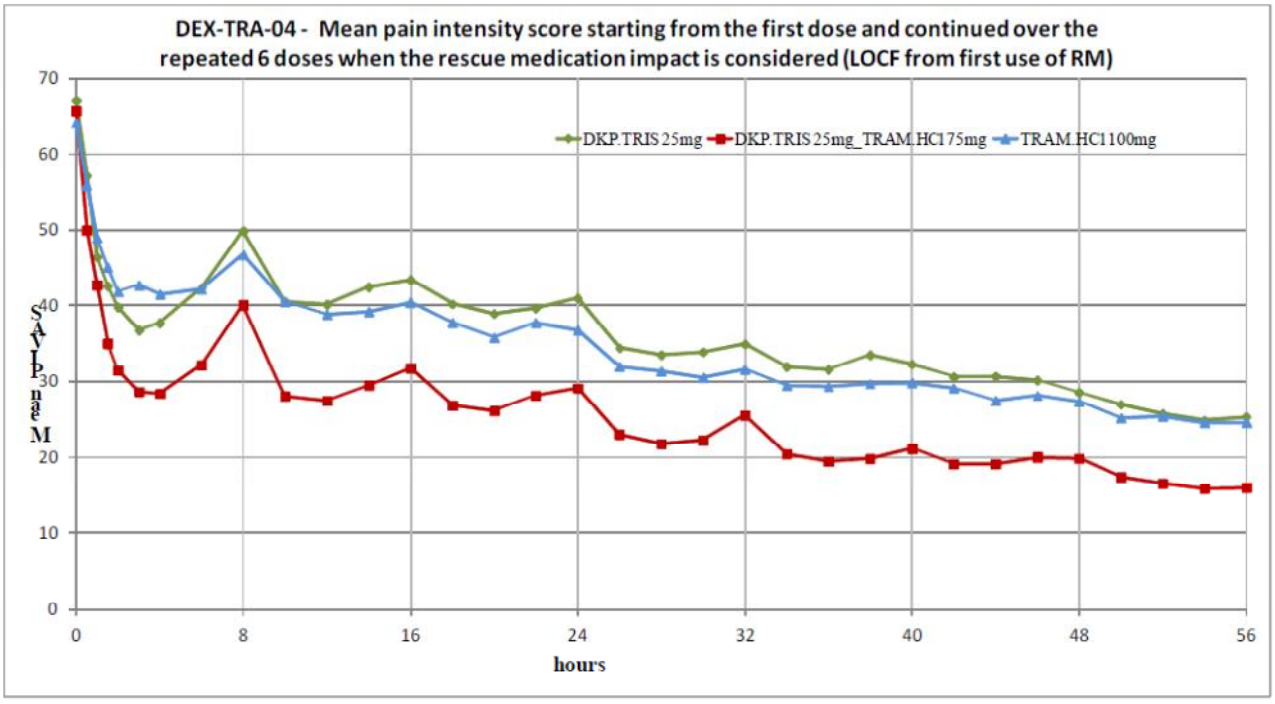
Table 2b DEX-TRA-04 (Visceral pain model) - DKP.TRIS 25 mg/TRAM.HCl 75 mg vs TRAM.HCl 100 mg: Impact of RM analysis by time-point and over 0-8, 0-24, 0-32 and 0-56 - (mITT population)

Timepoint (hours)	DKP.TRIS 25mg/TRAM_HCl_75mg Mean PI-VAS (SD)	TRAM.HCl 100mg Mean PI-VAS (SD)	Punctual difference mean	Estimated difference mean (SE)	P-value
2	31.6 (23.32)	41.9 (24.53)	-10.3	-10.2 (2.69)	0.0002
4	28.4 (22.78)	41.5 (26.02)	-13.1	-13.0 (2.71)	<.0001
6	32.2 (23.80)	42.2 (25.24)	-10.0	-9.8 (2.69)	0.0003
8	40.1 (25.99)	46.8 (24.72)	-6.7	-6.6 (2.80)	0.0190
10	28.1 (24.47)	40.5 (23.98)	-12.5	-12.3 (2.70)	<.0001
12	27.4 (25.44)	38.9 (25.05)	-11.5	-11.4 (2.83)	<.0001
14	29.5 (25.12)	39.3 (24.27)	-9.8	-9.7 (2.79)	0.0006
16	31.8 (25.52)	40.4 (25.31)	-8.6	-8.5 (2.88)	0.0033
18	26.8 (23.89)	37.8 (26.29)	-11.0	-10.9 (2.91)	0.0002
20	26.1 (24.23)	35.9 (25.76)	-9.8	-9.7 (2.85)	0.0007
22	28.1 (23.36)	37.8 (24.45)	-9.7	-9.6 (2.74)	0.0005
24	29.2 (23.79)	36.8 (25.14)	-7.6	-7.5 (2.81)	0.0076
26	23.0 (23.91)	32.0 (25.22)	-8.9	-8.9 (2.88)	0.0023
28	21.8 (23.89)	31.4 (26.02)	-9.6	-9.5 (2.91)	0.0012
30	22.2 (23.53)	30.6 (25.45)	-8.3	-8.2 (2.89)	0.0046
32	25.6 (24.26)	31.6 (26.31)	-6.1	-6.0 (2.97)	0.0443
34	20.5 (23.49)	29.5 (26.41)	-8.9	-8.9 (2.96)	0.0029
36	19.5 (23.50)	29.3 (26.29)	-9.8	-9.8 (2.98)	0.0012
38	19.8 (23.25)	29.7 (26.71)	-9.8	-9.8 (3.00)	0.0012
40	21.2 (24.48)	29.8 (26.95)	-8.7	-8.6 (3.04)	0.0048
42	19.2 (23.92)	29.1 (27.09)	-10.0	-9.9 (3.05)	0.0012
44	19.2 (23.65)	27.5 (26.69)	-8.3	-8.2 (3.00)	0.0063
46	20.1 (24.08)	28.1 (26.48)	-8.1	-8.0 (3.00)	0.0078
48	19.9 (24.44)	27.3 (26.87)	-7.4	-7.3 (3.05)	0.0166
50	17.4 (24.70)	25.2 (27.17)	-7.7	-7.7 (3.08)	0.0128
52	16.6 (24.27)	25.4 (27.20)	-8.8	-8.7 (3.07)	0.0046
54	15.9 (24.12)	24.6 (27.14)	-8.6	-8.6 (3.05)	0.0049
56	16.1 (24.11)	24.6 (27.94)	-8.5	-8.5 (3.09)	0.0064
0 -8	**33.1 (4.99)**	**43.1 (2.48)**	**-10.0**	**-9.9 (1.36)**	**<.0001**
0-24	**29.9 (3.77)**	**40.0 (2.95)**	**-10.1**	**-9.9 (0.80)**	**<.0001**
0-32	**28.2 (4.48)**	**37.8 (4.60)**	**-9.6**	**-9.5 (0.70)**	**<.0001**
0-56	**24.2 (5.93)**	**33.4 (6.37)**	**-9.2**	**-9.1 (0.55)**	**<.0001**

Table 4b **DEX-TRA-04 (Visceral pain model) - DKP.TRIS 25 mg/TRAM.HCl 75 mg vs DKP 25 mg:** Impact of RM analysis by time-point and over 0-8, 0-24, 0-32 and 0-56 - (mITT population)

Timepoint hours	DKP.TRIS 25mg/TRAM.HCl 75mg Mean PI-VAS (SD)*	DKP. TRIS 25mg Mean PI-VAS (SD)*	Punctual difference mean	Estimated difference mean (SE)	P-value
2	31.6 (23.32)	39.8 (25.28)	-8.2	-8.2 (2.68)	0.0025
4	28.4 (22.78)	37.7 (24.64)	-9.3	-9.3 (2.70)	0.0006
6	32.2 (23.80)	42.4 (24.44)	-10.2	-10.1 (2.68)	0.0002
8	40.1 (25.99)	49.9 (24.25)	-9.8	-9.8 (2.79)	0.0005
10	28.1 (24.47)	40.6 (24.93)	-12.5	-12.5 (2.69)	<.0001
12	27.4 (25.44)	40.2 (26.25)	-12.8	-12.7 (2.83)	<.0001
14	29.5 (25.12)	42.4 (25.96)	-13.0	-12.9 (2.79)	<.0001
16	31.8 (25.52)	43.4 (26.37)	-11.6	-11.5 (2.87)	<.0001
18	26.8 (23.89)	40.2 (27.52)	-13.4	-13.4 (2.91)	<.0001
20	26.1 (24.23)	39.0 (26.55)	-12.9	-12.8 (2.85)	<.0001
22	28.1 (23.36)	39.7 (25.64)	-11.6	-11.5 (2.73)	<.0001
24	29.2 (23.79)	41.0 (26.27)	-11.8	-11.8 (2.81)	<.0001
26	23.0 (23.91)	34.5 (27.31)	-11.4	-11.4 (2.88)	<.0001
28	21.8 (23.89)	33.5 (27.26)	-11.7	-11.7 (2.90)	<.0001
30	22.2 (23.53)	33.9 (27.57)	-11.7	-11.7 (2.88)	<.0001
32	25.6 (24.26)	35.0 (27.73)	-9.4	-9.4 (2.96)	0.0017
34	20.5 (23.49)	32.0 (28.00)	-11.5	-11.5 (2.96)	0.0001
36	19.5 (23.50)	31.6 (28.61)	-12.1	-12.1 (2.98)	<.0001
38	19.8 (23.25)	33.5 (28.62)	-13.7	-13.7 (2.99)	<.0001
40	21.2 (24.48)	32.3 (28.28)	-11.2	-11.1 (3.04)	0.0003
42	19.2 (23.92)	30.6 (28.56)	-11.5	-11.5 (3.05)	0.0002
44	19.2 (23.65)	30.7 (28.19)	-11.5	-11.5 (3.00)	0.0001
46	20.1 (24.08)	30.2 (27.79)	-10.1	-10.1 (2.99)	0.0008
48	19.9 (24.44)	28.6 (28.40)	-8.7	-8.6 (3.05)	0.0049
50	17.4 (24.7)	27.0 (28.42)	-9.5	-9.5 (3.07)	0.0021
52	16.6 (24.27)	25.7 (28.56)	-9.1	-9.1 (3.07)	0.0032
54	15.9 (24.12)	24.9 (28.17)	-8.9	-8.9 (3.04)	0.0036
56	16.1 (24.11)	25.3 (28.34)	-9.3	-9.2 (3.08)	0.0029
0 -8	**33.1 (4.99)**	**42.5 (5.32)**	**-9.4**	**-9.3 (1.36)**	**<.0001**
0-24	**29.9 (3.77)**	**41.4 (3.12)**	**-11.5**	**-11.4 (0.80)**	**<.0001**
0-32	**28.2 (4.48)**	**39.6 (4.17)**	**-11.4**	**-11.3 (0.70)**	**<.0001**
0-56	**24.2 (5.93)**	**35.2 (6.30)**	**-11.0**	**-11.0 (0.55)**	**<.0001**

Figure 1



DEX-TRA-05 ï PI-VAS over single dose (0-8 hours) and multiple dose phases (8-56 hours)

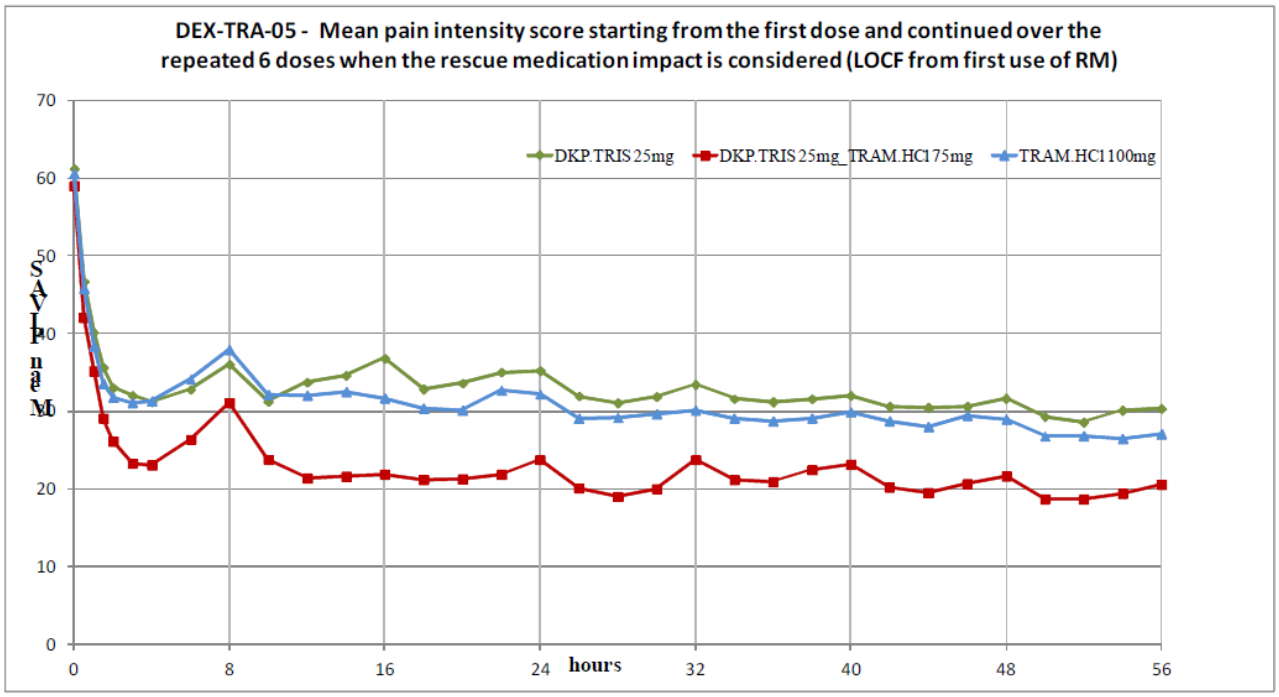
Table 3b DEX-TRA-05 (Somatic pain model) - DKP.TRIS 25 mg/TRAM.HCl 75 mg vs TRAM.HCl 100 mg: Impact of RM analysis by time-point and over 0-8, 0-24, 0-32 and 0-56 - (mITT population)

Timepoint hours	DKP.TRIS 25mg/TRAM_HCl 75mg Mean PI-VAS (SD)	TRAM.HCl 100mg Mean PI-VAS (SD)	Punctual difference mean	Estimated difference mean (SE)	P-value
2	26.1 (21.95)	31.8 (20.76)	--5.7	-5.6 (2.41)	0.0204
4	23.0 (22.16)	31.3 (21.91)	-8.3	-8.2 (2.51)	0.0011
6	26.4 (22.59)	34.1 (22.51)	-7.7	-7.7 (2.57)	0.0031
8	31.1 (23.43)	37.9 (24.16)	-6.8	-6.8 (2.70)	0.0122
10	23.8 (21.29)	32.2 (23.84)	-8.1	-8.3 (2.60)	0.0014
12	21.4 (20.23)	32.0 (23.36)	-9.4	-10.6 (2.59)	<.0001
14	21.6 (20.38)	32.5 (24.82)	-9.9	-10.9 (2.65)	<.0001
16	21.9 (19.92)	31.7 (24.48)	-8.6	-9.8 (2.64)	0.0002
18	21.2 (21.00)	30.3 (24.12)	-7.3	-9.1 (2.71)	0.0008
20	21.2 (20.56)	30.1 (24.69)	-5.3	-8.9 (2.72)	0.0012
22	21.8 (20.74)	32.7 (24.99)	-7.8	-10.8 (2.75)	<.0001
24	23.7 (21.80)	32.2 (25.66)	-6.1	-8.4 (2.76)	0.0023
26	20.1 (21.52)	29.0 (25.76)	-6.0	-8.9 (2.78)	0.0014
28	19.0 (20.54)	29.1 (25.18)	-7.5	-10.1 (2.74)	0.0002
30	20.0 (21.36)	29.6 (25.99)	-6.9	-9.6 (2.78)	0.0006
32	23.7 (22.05)	30.1 (25.59)	-4.1	-6.4 (2.75)	0.0210
34	21.2 (21.81)	29.1 (25.50)	-5.2	-7.9 (2.78)	0.0047
36	20.9 (21.61)	28.7 (25.55)	-4.5	-7.8 (2.75)	0.0049
38	22.4 (22.03)	29.1 (25.85)	-3.8	-6.7 (2.79)	0.0170
40	23.1 (20.46)	29.9 (25.57)	-4.1	-6.7 (2.74)	0.0142
42	20.2 (21.09)	28.8 (25.05)	-6.4	-8.5 (2.73)	0.0020
44	19.5 (21.61)	28.0 (25.07)	-5.8	-8.5 (2.76)	0.0023
46	20.6 (20.88)	29.4 (25.23)	-5.7	-8.8 (2.73)	0.0014
48	21.6 (22.73)	29.0 (25.73)	-5.6	-7.3 (2.82)	0.0101
50	18.7 (22.70)	26.8 (25.94)	-5.5	-8.1 (2.87)	0.0052
52	18.6 (23.00)	26.8 (26.00)	-5.3	-8.2 (2.87)	0.0045
54	19.4 (23.21)	26.5 (25.52)	-4.5	-7.0 (2.84)	0.0141
56	20.6 (22.85)	27.0 (25.77)	-4.5	-6.4 (2.82)	0.0234
0-8	**26.7 (3.33)**	**33.8 (3.03)**	**-7.1**	**-7.1 (1.27)**	**<.0001**
0-24	**23.6 (2.98)**	**32.4 (2.03)**	**-8.8**	**-8.8 (0.76)**	**<.0001**
0-32	**22.9 (3.01)**	**31.7 (2.18)**	**-8.8**	**-8.8 (0.67)**	**<.0001**
0-56	**21.9 (2.68)**	**30.2 (2.49)**	**-8.3**	**-8.3 (0.51)**	**<.0001**

Table 5b **DEX-TRA-05 (Somatic pain model) - DKP.TRIS 25 mg/TRAM.HCl 75 mg vs DKP 25 mg:** Impact of RM analysis by time-point and over 0-8, 0-24, 0-32 and 0-56 - (mITT population)

Timepoint hours	DKP.TRIS 25mg/TRAM.HCl 75mg Mean PI-VAS (SD)*	DKP.TRIS 25mg Mean PI-VAS (SD)	Punctual difference mean	Estimated difference mean (SE)	P-value
2	26.1 (21.95)	33.0 (23.53)	-6.9	-6.9 (2.41)	0.0041
4	23.0 (22.16)	31.2 (24.71)	-8.2	-8.2 (2.51)	0.0012
6	26.4 (22.59)	32.8 (25.15)	-6.4	-6.4 (2.57)	0.0131
8	31.1 (23.43)	36.0 (25.81)	-4.9	-4.7 (2.70)	0.0827
10	23.8 (21.29)	31.3 (25.55)	-7.5	-7.5 (2.60)	0.0043
12	21.4 (20.23)	33.7 (26.54)	-12.4	-12.5 (2.59)	<.0001
14	21.6 (20.38)	34.6 (26.34)	-13.0	-12.9 (2.65)	<.0001
16	21.9 (19.92)	36.8 (26.97)	-14.9	-14.8 (2.64)	<.0001
18	21.2 (21.00)	32.8 (28.11)	-11.7	-11.8 (2.71)	<.0001
20	21.2 (20.56)	33.6 (28.26)	-12.4	-12.1 (2.72)	<.0001
22	21.8 (20.74)	35.0 (28.44)	-13.2	-13.3 (2.75)	<.0001
24	23.7 (21.80)	35.2 (27.66)	-11.5	-11.6 (2.76)	<.0001
26	20.1 (21.52)	31.9 (28.26)	-11.9	-11.9 (2.78)	<.0001
28	19.0 (20.54)	31.1 (28.09)	-12.1	-12.3 (2.74)	<.0001
30	20.0 (21.36)	31.9 (27.89)	-11.9	-12.0 (2.78)	<.0001
32	23.7 (22.05)	33.4 (27.59)	-9.7	-9.8 (2.75)	0.0004
34	21.2 (21.81)	31.6 (27.87)	-10.4	-10.6 (2.78)	0.0002
36	20.9 (21.61)	31.2 (27.32)	-10.3	-10.5 (2.75)	0.0002
38	22.4 (22.03)	31.6 (27.44)	-9.2	-9.3 (2.79)	0.0009
40	23.1 (20.46)	32.0 (27.79)	-8.9	-9.0 (2.74)	0.0011
42	20.2 (21.09)	30.6 (27.47)	-10.4	-10.5 (2.73)	0.0001
44	19.5 (21.61)	30.4 (27.71)	-11.0	-11.1 (2.76)	<.0001
46	20.6 (20.88)	30.6 (27.48)	-10.0	-10.1 (2.73)	0.0002
48	21.6 (22.73)	31.6 (28.01)	-10.0	-10.1 (2.82)	0.0004
50	18.7 (22.70)	29.3 (28.83)	-10.6	-10.8 (2.87)	0.0002
52	18.6 (23.00)	28.6 (28.58)	-10.0	-10.1 (2.87)	0.0005
54	19.4 (23.21)	30.1 (28.30)	-10.7	-10.8 (2.84)	0.0002
56	20.6 (22.85)	30.3 (27.85)	-9.8	-9.9 (2.82)	0.0005
0-8	**26.7 (3.33)**	**33.3 (2.01)**	**-6.6**	**-6.6 (1.27)**	**<.0001**
0-24	**23.6 (2.98)**	**33.8 (1.75)**	**-10.2**	**-10.2 (0.76)**	**<.0001**
0-32	**22.9 (3.01)**	**33.4 (1.75)**	**-10.5**	**-10.5 (0.67)**	**<.0001**
0-56	**21.9 (2.68)**	**32.2 (2.00)**	**-10.3**	**-10.4 (0.51)**	**<.0001**

Figure 2



The broad indication (symptomatic short term treatment of moderate to severe acute pain) is considered acceptable since the superiority in efficacy of the combination versus the monocomponents is considered to be demonstrated on both pain model (somatic and visceral).

However the inclusion of a limitation of treatment duration was considered based on safety data available. Treatment duration not exceeding 5 days was included under section 4.2 of SmPC.

Regarding the inclusion of placebo in a pain study as the ones herewith assessed, which is highly recommended so as to check the internal validity, given the necessity of confirming that active comparators are working as they are expected. In this sense, the inclusion of placebo in the multiple-dose phase was discussed and recommended in the scientific advice given by the RMS. The uncertain due to the lack of placebo in the multiple-dose phase could be, to some extent, partially resolved considering that in the single dose phase, the placebo was included and statistically significant and clinically relevant differences were observed between placebo and mono-components. In addition, in the multiple dose phase, the behaviour of both components is quite similar, which would be suggesting the different behaviour regarding the placebo. It should be noted that data from single dose and multiple-dose come from the same study and same patients, or in others words, it is reasonable to expect the same pattern for the mono-components in the multiple-dose phase. For all above, it would not be realistic that the inclusion of placebo had shown an unexpected behaviour of mono-components in the multiple-dose phase. The acute phase (first 24 hours) is clearly pointing out the superiority of the combination versus the mono-components, which are also superior to placebo is this phase.

CLINICAL SAFETY

From a safety point of view, the safety profile of combination appears overall similar to monocomponents, with the exception of serious TESS (Treatment Emergent Signs and Symptoms) in phase III studies - multiple-dose phase, which is higher with the combination.

Single data and multiple dose data from the pooled phase III trials is shown below:

Table 2.7.4.10. Phase III. (single-dose phase). Overview of TESS and ADR, by treatment group and overall, expressed as number of patients (%)|number of events.

	Placebo n=314	DKP25/TRAM75 n=310	DKP.TRIS 25mg n=313	TRAM.HCl 100mg n=310	Overall N=1247
Overall TESS	**27(8.6%)|32**	**22(7.1%)|24**	**22(7.0%)|22**	**31(10.0%)|42**	**102(8.2%)|120**
mild	*19(6.1%)|23*	*14(4.5%)|14*	*12(3.8%)|12*	*21(6.8%)|27*	*66 (5.3%)|76*
moderate	*8(2.5%) 8*	*9(2.9%)|10*	*8(2.6%)|8*	*12(3.9%)|14*	*37 (3.0%)|40*
severe	*1(0.3%)|1*	-	*2(0.6%)|2*	*1(0.3%)|1*	*4 (0.3%)|4*
Serious TESS	-	**1(0.3%)|1**	**1(0.3%)|1**	-	**2(0.2%)|2**
TESS leading to discontinuation	**1(0.3%)|1**	**2(0.6%)|3**	**4(1.3%)|4**	-	**7(0.6%)|8**
TESS leading to death	-	-	-	-	-
Overall ADR	**8(2.5%)|8**	**3(1.0%)|4**	**10(3.2%)|10**	**15(4.8%)|20**	**36(2.9%)|42**
mild	*7(2.2%)|7*	*1(0.3%)|1*	*4(1.3%)|4*	*7(2.3%)|9*	*19 (1.5%)|21*
moderate	*1(0.3%)|1*	*2(0.6%)|3*	*5(1.6%)|5*	*10(3.2%)|11*	*18 (1.4%)|20*
severe	-	-	*1(0.3%)|1*	-	*1 (0.1%)|1*
Serious ADR	-	-	-	-	-
ADR leading to discontinuation	-	**1(0.3%)|2**	**2(0.6%)|2**	-	**3(0.2%)|4**

Source data: Pooled Analysis for DKP/TRAM studies (Table 5.7 and Table 5.10); DEX-TRA-04 CSR (Table 14.3.2.4), DEX-TRA-05 CSR (Table 14.3.2.4). NOTE: Two patients from the DEX-TRA-04 study (one allocated to DKP.TRIS and another one allocated to placebo) discontinued prematurely due to lack of efficacy, however the TESS "procedural pain" and "pain", respectively were also reported as reason for withdrawal) and for this reason these patients are included in the table.

Table 2.7.4.9. Phase III (active treatment). Overview of TESS and ADR, by treatment group and overall, expressed as number of patients (%)|number of events.

	DKP25/TRAM75 n=416	DKP.TRIS 25mg n=416	TRAM.HCl 100mg n=415	Overall N=1247
Overall TESS	**110(26.4%)|149**	**117(28.1%)|170**	**128(30.8%)|192**	**355(28.5%)|511**
mild	*74(17.8%)|90*	*82(19.7%)|110*	*98(23.6%)|131*	*254(20.4%)|331*
moderate	*40(9.6%)|49*	*42(10.1%)|51*	*43(10.4%)|52*	*125(10.0%)|152*
severe	*5(1.2%)|10*	*6(1.4%)|9*	*7(1.7%)|9*	*18(1.4%)|28*
Serious TESS	**10(2.4%)|17**	**5(1.2%)|6**	**3(0.7%)|6**	**18(1.4%)|29**
TESS leading to discontinuation	**7(1.7%)|12**	**7(1.7%)|7**	**6(1.4%)|6**	**20(1.6%)|25**
TESS leading to death	-	-	-	-
Overall ADR	**25(6.0%)|36**	**40(9.6%)|51**	**38(9.2%)|52**	**103(8.3%)|139**
mild	*10(2.4%)|13*	*21(5.0%)|27*	*24(5.8%)|27*	*55(4.4%)|67*
moderate	*13(3.6%)|18*	*17(4.1%)|19*	*19(4.6%)|23*	*51(4.1%)|60*
severe	*2(0.5%)|5*	*3(0.7%)|5*	*2(0.5%)|2*	*7(0.6%)|12*
Serious ADR	**2(0.5%)|5**	*1(0.2%)|1*	-	**3(0.2%)|6**
ADR leading to discontinuation	**4(1.0%)|9**	**4(1.0%)|4**	**3(0.7%)|3**	**11(0.9%)|16**

Source data: Pooled Analysis for DKP/TRAM studies (Table 5.1 and Table 5.4), DEX-TRA-04 CSR (Table 14.3.2.3), DEX-TRA-05 CSR (Table 14.3.2.3). NOTES: "Active treatment" refers to TESS arising after first dose of active drug intake (i.e. DKP/TRAM, DKP.TRIS or TRAM.HCl); For the phase III studies (active treatment), throughout the document, the number of patients in each group of treatment includes the 10 patients that received placebo during the single-dose phase and discontinued the study prematurely before entering the multiple-dose phase. Although these patients were intended to receive DKP/TRAM (3 patients), DKP.TRIS (3 patients) and TRAM.HCl (4 patients) during the multiple-dose phase, they received placebo only during the study. In the DEX-TRA-04 study, one event experienced by one patient in the TRAM.HCl group was upgraded to serious ("other important medical condition") by the Sponsor; therefore the table displays one additional serious TESS that is not included in the DEX-TRA-04 CSR Table 14.3.3.5 but in the Sponsor Local Safety Data Base. One patient from the DEX-TRA-04, allocated to DKP.TRIS, discontinued prematurely due to lack of efficacy, however the TESS "procedural pain" was also reported as reason for withdrawal and for this reason the patient is included in the table.

DEX-TRA-02

Table 12-3: Overview of TESSs, by treatment and overall (safety population), expressed as number of patients (%) | number of events

	DKP 12.5mg + TRAM 37.5mg	DKP 12.5mg + TRAM 75mg	DKP 25mg + TRAM 37.5mg	DKP 25mg + TRAM 75mg	DKP 12.5mg	DKP 25mg	TRAM 37.5mg	TRAM 75mg	Ibuprofen	Placebo	Overall
	n=61	n=63	n=63	n=61	n=60	n=61	n=59	n=60	n=61	n=62	n=611
Overall	12(19.7)| 24	15(23.8)| 25	10(15.9)| 16	19(31.1)| 33	12(20.0)| 14	10(16.4)| 11	12(20.3)| 19	22(36.7)| 44	12(19.7)| 16	10(16.1)| 11	134(21.9)| 213
Intensity											
Mild	8(13.1)| 12	10(15.9)| 15	8(12.7)| 10	15(24.6)| 28	6(10.0)| 7	7(11.5)| 8	7(11.9)| 12	15(25.0)| 23	6(9.8)| 8	8(12.9)| 9	90(14.7)| 132
Moderate	6(9.8)| 10	7(11.1)| 8	4(6.3)| 4	3(4.9)| 3	5(8.3)| 6	3(4.9)| 3	4(6.8)| 5	11(18.3)| 20	6(9.8)| 7	1(1.6)| 1	50(8.2)| 67
Severe	2(3.3)| 2	2(3.2)| 2	1(1.6)| 2	2(3.3)| 2	1(1.7)| 1	0	2(3.4)| 2	1(1.7)| 1	1(1.6)| 1	1(1.6)| 1	13(2.1)| 14
Causality											
Certainly related	0	0	0	1(1.6)| 1	0	0	1(1.7)| 1	1(1.7)| 1	1(1.6)| 1	0	4(0.7)| 4
Probably related	0	4(6.3)| 6	0	2(3.3)| 3	0	0	1(1.7)| 1	1(1.7)| 1	1(1.6)| 1	0	9(1.5)| 12
Possibly related	3(4.9)| 6	2(3.2)| 2	4(6.3)| 4	4(6.6)| 9	1(1.7)| 1	3(4.9)| 4	1(1.7)| 1	8(13.3)| 15	2(3.3)| 2	0	28(4.6)| 44
Unlikely related	1(1.6)| 1	2(3.2)| 6	3(4.8)| 6	3(4.9)| 3	1(1.7)| 1	3(4.9)| 3	2(3.4)| 5	2(3.3)| 5	3(4.9)| 4	3(4.8)| 3	23(3.8)| 37
Not related	8(13.1)| 17	8(12.7)| 10	5(7.9)| 6	12(19.7)| 17	12(20.0)| 12	4(6.6)| 4	9(15.3)| 11	15(25.0)| 20	7(11.5)| 8	8(12.9)| 8	88(14.4)| 113
Unassessable / unclassifiable	0	1(1.6)| 1	0	0	0	0	0	1(1.7)| 2	0	0	2(0.3)| 3
SAE	0	0	0	0	0	0	0	1(1.7)| 1*	0	0	1(0.2)| 1

AEs were considered as TESS if they occurred for the first time or if they worsened in terms of seriousness or severity after the study drug administration on Visit 2; TESSs were considered as treatment-related (ADR) if they were at least "possibly related" to the study drug, according to the criteria stated in § 9.5.1.4.5. Cases in which the causality was classified by the Investigator as "unassessable/unclassifiable" were also considered ADR. (*) Only 1 serious TESS was reported in 1 patient allocated to the TRAM 75mg group, which was assessed as "possibly related"; Source data: Table 4.2.2; Appendix 16.1.9.2.

Table 12-4: Overview of ADRs, by treatment and overall (safety population), expressed as number of patients (%) | number of events

	DKP 12.5mg + TRAM 37.5mg	DKP 12.5mg + TRAM 75mg	DKP 25mg + TRAM 37.5mg	DKP 25mg + TRAM 75mg	DKP 12.5mg	DKP 25mg	TRAM 37.5mg	TRAM 75mg	Ibuprofen	Placebo	Overall
	n=61	n=63	n=63	n=61	n=60	n=61	n=59	n=60	n=61	n=62	n=611
Overall	3 (4,9)| 6	6 (9,5)| 9	4 (6,3)| 4	7 (11,5)| 13	1 (1,7)| 1	3 (4,9)| 4	3 (5,1)| 3	10 (16,7) | 19	3 (4,9) | 4	0	40 (6,5) | 63
Intensity											
Mild	1(1.6)| 2	4(6.3)| 5	3(4.8)| 3	7(11.5)| 13	1(1.7)| 1	2(3.3)| 3	3(5.1)| 3	7(11.7)| 11	3(4.9)| 4	0	31(5.1)| 45
Moderate	2(3.3)| 4	3(4.8)| 3	1(1.6)| 1	0	0	1(1.6)| 1	0	5(8.3)| 8	0	0	12(2.0)| 17
Severe	0	1(1.6)| 1	0	0	0	0	0	0	0	0	1(0.2)| 1
Causality											
Certainly related	0	0	0	1(1.6)| 1	0	0	1(1.7)| 1	1(1.7)| 1	1(1.6)| 1	0	4(0.7)| 4
Probably related	0	4(6.3)| 6	0	2(3.3)| 3	0	0	1(1.7)| 1	1(1.7)| 1	1(1.6)| 1	0	9(1.5)| 12
Possibly related	3(4.9)| 6	2(3.2)| 2	4(6.3)| 4	4(6.6)| 9	1(1.7)| 1	3(4.9)| 4	1(1.7)| 1	8(13.3)| 15	2(3.3)| 2	0	28(4.6)| 44
Unassessable / unclassifiable	0	1(1.6)| 1	0	0	0	0	0	1(1.7)| 2	0	0	2(0.3)| 3
SADR	0	0	0	0	0	0	0	1(1.7)| 1	0	0	1(0.2)| 1

Additional clarification was requested regarding serious TESS. The number of serious TESS and serious ADRs are low, making hard any comparison among treatments. Eighteen (1.4%) patients experienced a total of 29 events in DEX-TRAM-04 and DEX-TRAM-05. In addition, after single dose, the increase in serious TESS with the combination is not observed (phase III-single dose or DEX-TRAM-02). Additionally, in DEX-TRAM-04 with 3 days of treatment the differences are higher than in DEX-TRAM-05 with 5 days. The relation between the combination and serious TESS is not clear. Therefore, at this time, with available data, the safety profile is considered similar.

Overall Summary of TESS during Active Treatment ï Safety Population (DEX-TRAM-04)

Category	DKP.TRIS+ TRAM.HCl (N=203)		DKP.TRIS (N=202)		TRAM.HCl (N=201)		Overall (N=606)	
	N AE	n (%)	N AE	n (%)	N AE	n (%)	N AE	n (%)
Any TESS	81	57 (28.1)	101	69 (34.2)	111	75 (37.3)	293	201 (33.2)
Any serious TESS	9	7 (3.4)	2	2 (1.0)	3	1 (0.5)	14	10 (1.7)
Any mild TESS	44	34 (16.7)	61	46 (22.8)	71	55 (27.4)	176	135 (22.3)
Any moderate TESS	35	28 (13.8)	34	27 (13.4)	34	27 (13.4)	103	82 (13.5)
Any severe TESS	2	2 (1.0)	6	4 (2.0)	6	4 (2.0)	14	10 (1.7)
Any causally-related TESS	26	19 (9.4)	39	30 (14.9)	35	27 (13.4)	100	76 (12.5)
Any TESS leading to discontinuation	5	4 (2.0)	6	6 (3.0)	1	1 (0.5)	12	11 (1.8)
Any TESS leading to death	0	0	0	0	0	0	0	0

Source: Section 14, Table 14.3.2.3
Note: TESS during active treatment do not include TESS occurred during the single-dose phase for placebo-treated patients,
Abbreviations: AE=Adverse Event; DKP.TRIS=Dexketoprofen Trometamol; N=Number of Patients in Treatment Group, n=Number of Patients with an Observation; N AE=Number of Adverse Events; TESS=Treatment-Emergent Sign and Symptoms; TRAM.HCl=Tramadol Hydrochloride

Overall Summary of TESS during Active Treatment ï Safety Population (DEX-TRAM-05)

Category	DKP.TRIS+ TRAM.HCl (N=213)		DKP.TRIS (N=214)		TRAM.HCl (N=214)		Overall (N=641)	
	N AE	n (%)	N AE	n (%)	N AE	n (%)	N AE	n (%)
Any TESS	68	53 (24.9)	69	48 (22.4)	81	53 (24.8)	218	154 (24.0)
Any Serious TESS	8	3 (1.4)	4	3 (1.4)	2	1 (0.5)	14	7 (1.1)
Any Mild TESS	46	40 (18.8)	49	36 (16.8)	60	43 (20.1)	155	119 (18.6)
Any Moderate TESS	14	12 (5.6)	17	15 (7.0)	18	16 (7.5)	49	43 (6.7)
Any Severe TESS	8	3 (1.4)	3	2 (0.9)	3	3 (1.4)	14	8 (1.2)
Any Causally Related TESS	10	6 (2.8)	12	10 (4.7)	17	11 (5.1)	39	27 (4.2)
Any TESS Leading to Discontinuation	7	3 (1.4)	1	1 (0.5)	5	5 (2.3)	13	9 (1.4)
Any TESS Leading to Death	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)

Source: Section 14, Table 14.3.2.3
Abbreviations: DKP.TRIS=Dexketoprofen Trometamol; N=number of patients in treatment group, n=number of patients with an observation; N AE=number of adverse events; TESS=treatment emergent signs and symptoms; TRAM.HCl=Tramadol Hydrochloride

OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Enanplus 75 mg/25 mg film-coated tablets and Takudex 75 mg/25 mg film-coated tablets, in the treatment of symptomatic short term treatment of moderate to severe acute pain in adult patients whose pain is considered to require a combination of tramadol and dexketoprofen is approvable.

The benefit/risk balance was considered to be positive.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in January 2016.