Clinical trial results:
A randomized, double-blind, placebo and active-controlled, parallel-group study to evaluate the analgesic efficacy and safety of dexketoprofen trometamol and tramadol hydrochloride oral fixed combination on moderate to severe acute pain after elective unilateral total hip arthroplasty.

Summary

EudraCT number	2012-004548-31
Trial protocol	CZ ES HU LV LT PL
Global end of trial date	05 February 2014

Results information

Result version number	v1 (current)
This version publication date	25 March 2017
First version publication date	25 March 2017

Trial information

Trial identification

Sponsor protocol code	DEX-TRA-05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01902134
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Menarini Ricerche, S.p.A.
Sponsor organisation address	via sette santi, 1, Florence, Italy, 50131
Public contact	Clinical Research Corporate Director, Menarini Ricerche S.p.A., +39 05556809933, ACapriati@menarini-ricerche.it
Scientific contact	Clinical Research Corporate Director, Menarini Ricerche S.p.A., +39 05556809933, ACapriati@menarini-ricerche.it

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 February 2014
Global end of trial reached?	Yes
Global end of trial date	05 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the analgesic efficacy of oral dexketoprofen trometamol (DKP.TRIS) and tramadol hydrochloride (TRAM.HCl) fixed combination on moderate to severe pain after elective hip arthroplasty.

Protection of trial subjects:

If any event(s) related to the conduct of the study or the development of 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 IRB/ECs will be informed forthwith about these new events and the measures taken.

For patients participating in the study, 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 made available to patients in the ICF and/or provided as a separate document, in accordance with national requirements.

According to the results from phase I and phase II studies, the tested fixed-combination is expected to provide adequate pain relief for the participating patients without raising any safety concerns. In addition, patients will be hospitalized for the entire study treatment duration and monitoring of AEs will be conducted during this period. Upon discharge, they will be instructed to contact the site immediately in case of any medical emergency.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	30 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Serbia: 62
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Ukraine: 56
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Czech Republic: 36
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 204
Country: Number of subjects enrolled	Latvia: 153
Country: Number of subjects enrolled	Lithuania: 84

Worldwide total number of subjects	641
EEA total number of subjects	516

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	367
From 65 to 84 years	274
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was screened on 30th April 2013 and; the first patient randomized on 7th May 2013. The last patient completed the study on 5th February 2014. The study was conducted at 44 study centers in 10 countries (Czech Republic, Germany, Hungary, Latvia, Lithuania, Poland, Serbia, Spain, Taiwan, and Ukraine).

Pre-assignment

Screening details:

A total of 746 patients were screened and 641 of them were randomized (screening failure rate: 14.1%). The enrollment was competitive.

Period 1

Period 1 title	Screening
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Screening

Arm description:

Screening period, for study eligibility assessment (within 4 weeks prior to randomization).
746 patients were screened and 105 of them were screening failure.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Screening
Started	641
Completed	641

Period 2

Period 2 title	Treatment and assessment period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Eligible patients were randomized in a 3:3:3:1:1:1 ratio to 1 of the 6 possible treatment arms, as per treatment code assigned by IVRS/IWRS in accordance with the randomisation list. DKP/TRAM and DKP were provided as film-coated tablet with matching appearance and weight. TRAM as two capsules of a marketed drug Contramal® 50mg. Placebos matching with both pharmaceutical forms were available to

secure double-blind conditions by using a double-dummy technique.

Arms

Are arms mutually exclusive?	Yes
Arm title	DKP/TRAM followed by DKP/TRAM

Arm description:

Single-dose phase: Patients received DKP.TRIS 25mg + TRAM.HCl 75mg.
Single-dose treatment had to be administered on day 1.

Multiple-dose phase: Patients received DKP.TRIS 25mg + TRAM.HCl 75mg.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations (every 8 hours).

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Arm type	Experimental
Investigational medicinal product name	DKP/TRAM
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

DKP.TRIS 25mg + TRAM.HCl 75mg
Treatment had to be orally administered, together with approximately 150 mg of still/tap water.

Arm title	DKP followed by DKP

Arm description:

Single-dose phase: Patients received DKP.TRIS 25mg.
Single dose treatment had to be administered on day 1.

Multiple-dose phase: Patients received DKP.TRIS 25mg.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations (every 8 hours).

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Arm type	Active comparator
Investigational medicinal product name	DKP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

DKP.TRIS 25mg
Treatment had to be orally administered, together with approximately 150 ml of still/tap water.

Arm title	TRAM followed by TRAM

Arm description:

Single-dose phase: Patients received TRAM.HCl 100mg.
Single-dose treatment had to be administered on day 1.

Multiple-dose phase: Patients received TRAM.HCl 100mg.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations (every 8 hours).

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Arm type	Active comparator
Investigational medicinal product name	TRAM
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

TRAM.HCl 100mg
Treatment had to be orally administered, together with approximately 150ml of still/tap water.

Arm title	Placebo followed by DKP/TRAM

Arm description:

Single-dose phase: Patients received Placebo (as one tablet matching DKP.TRIS 25mg + TRAM.HCl 75mg and matching DKP.TRIS 25mg and as two capsules matching TRAM.HCl 50mg).

Multiple-dose phase: Placebo assigned patients were allocated to receive DKP.TRIS 25mg + TRAM.HCl 75mg, every 8 hours.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations.

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Arm type	Placebo + experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment had to be orally administered, together with approximately 150 ml of still/tap water.

Investigational medicinal product name	DKP/TRAM
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

DKP.TRIS 25mg + TRAM.HCl 75mg
Treatment had to be orally administered, together with approximately 150ml of still/tap water.

Arm title	Placebo followed by DKP

Arm description:

Single-dose phase: Patients received Placebo (as one tablet matching DKP.TRIS 25mg + TRAM.HCl 75mg and matching DKP.TRIS 25mg and as two capsules matching TRAM.HCl 50mg).

Multiple-dose phase: Placebo assigned patients were allocated to receive DKP.TRIS 25mg, every 8 hours.
Multiple-dose treatment had to be orally administered (starting 8 hours after single dose phase) up to the morning of day 5, for a total of 12 drug administrations.

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Arm type	Placebo + Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:	
Treatment had to be orally administered, together with approximately 150 ml of still/tap water.	
Investigational medicinal product name	DKP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Treatment had to be orally administered, together with approximately 150 ml of still/tap water.	
Arm title	Placebo followed by TRAM

Arm description:

Single-dose phase: Patients received Placebo (as one tablet matching DKP.TRIS 25mg + TRAM.HCl 75mg and matching DKP.TRIS 25mg and as two capsules matching TRAM.HCl).

Multiple-dose phase: Placebo assigned patients were allocated to receive two capsules of TRAM.HCl 50mg, every 8 hours.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations.

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Arm type	Placebo + Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Treatment had to be orally administered, together with approximately 150 ml of still/tap water.	
Investigational medicinal product name	TRAM
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Treatment had to be orally administered, together with approximately 150 ml of still/tap water.	

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The individual study participation included a screening period (period 1) for study eligibility assessment, a treatment and assessment period (period 2), where during the single-dose phase, PI-VAS at rest and PI-VAS on movement were recorded as beaseline, i.e. immediately prior to the time of the first study drug administration (t0). Finally a end of study visit (period 3) for final follow-up.

Number of subjects in period 2	DKP/TRAM followed by DKP/TRAM	DKP followed by DKP	TRAM followed by TRAM
Started	159	161	160
Completed	151	150	145
Not completed	8	11	15
Consent withdrawn by subject	4	8	9
Physician decision	-	1	-
Adverse event, non-fatal	3	1	2
NA	-	1	2

non compliance with study drug	1	-	-
lack of efficacy	-	-	2
Protocol deviation	-	-	-

Number of subjects in period 2	Placebo followed by DKP/TRAM	Placebo followed by DKP	Placebo followed by TRAM
Started	54	53	54
Completed	52	46	45
Not completed	2	7	9
Consent withdrawn by subject	1	5	4
Physician decision	-	-	-
Adverse event, non-fatal	1	1	3
NA	-	1	-
non compliance with study drug	-	-	-
lack of efficacy	-	-	1
Protocol deviation	-	-	1

Period 3

Period 3 title	End of study visit
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Treatment blinding was kept for the entire study duration up to the closure of database performed after the last patient last visit.

Arms

Arm title	End of study visit

Arm description:

Treatment blinidng was kept for the entire study duration un to the closure of database performed after the last patient last visit.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 3	End of study visit
Started	589
Completed	589

Baseline characteristics

Reporting groups

Reporting group title	DKP/TRAM followed by DKP/TRAM

Reporting group description:

Single-dose phase: Patients received DKP.TRIS 25mg + TRAM.HCl 75mg.
Single-dose treatment had to be administered on day 1.

Multiple-dose phase: Patients received DKP.TRIS 25mg + TRAM.HCl 75mg.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations (every 8 hours).

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Reporting group title	DKP followed by DKP

Reporting group description:

Single-dose phase: Patients received DKP.TRIS 25mg.
Single dose treatment had to be administered on day 1.

Multiple-dose phase: Patients received DKP.TRIS 25mg.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations (every 8 hours).

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Reporting group title	TRAM followed by TRAM

Reporting group description:

Single-dose phase: Patients received TRAM.HCl 100mg.
Single-dose treatment had to be administered on day 1.

Multiple-dose phase: Patients received TRAM.HCl 100mg.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations (every 8 hours).

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Reporting group title	Placebo followed by DKP/TRAM

Reporting group description:

Single-dose phase: Patients received Placebo (as one tablet matching DKP.TRIS 25mg + TRAM.HCl 75mg and matching DKP.TRIS 25mg and as two capsules matching TRAM.HCl 50mg).

Multiple-dose phase: Placebo assigned patients were allocated to receive DKP.TRIS 25mg + TRAM.HCl 75mg, every 8 hours.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations.

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Reporting group title	Placebo followed by DKP

Reporting group description:

Single-dose phase: Patients received Placebo (as one tablet matching DKP.TRIS 25mg + TRAM.HCl 75mg and matching DKP.TRIS 25mg and as two capsules matching TRAM.HCl 50mg).

Multiple-dose phase: Placebo assigned patients were allocated to receive DKP.TRIS 25mg, every 8 hours.
Multiple-dose treatment had to be orally administered (starting 8 hours after single dose phase) up to the morning of day 5, for a total of 12 drug administrations.

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Reporting group title	Placebo followed by TRAM

Reporting group description:

Single-dose phase: Patients received Placebo (as one tablet matching DKP.TRIS 25mg + TRAM.HCl 75mg and matching DKP.TRIS 25mg and as two capsules matching TRAM.HCl).

Multiple-dose phase: Placebo assigned patients were allocated to receive two capsules of TRAM.HCl 50mg, every 8 hours.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations.

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Reporting group values	DKP/TRAM followed by DKP/TRAM	DKP followed by DKP	TRAM followed by TRAM
Number of subjects	159	161	160
Age categorical Units: Subjects			
From 18 to 80 years	159	161	160
Age continuous Units: years			
geometric mean	61.3	63.3	61.3
standard deviation	± 10.43	± 9.01	± 9.68
Gender categorical Units: Subjects			
Female	86	86	80
Male	73	75	80
Race/Ethnicity, Customized Units: Subjects			
Asian	0	2	3
White	159	159	157
Region of Enrollment Units: Subjects			
Serbia	15	18	14
Taiwan	0	2	3
Czech Republic	9	10	8
Hungary	49	57	54
Spain	1	0	1
Poland	10	8	8
Ukraine	15	13	13
Lithuania	22	19	21
Germany	1	1	2
Latvia	37	33	36
Weight Units: kg			
arithmetic mean	83.3	81.4	83.5
standard deviation	± 15.37	± 15.63	± 17.25
Height Units: cm			
arithmetic mean	168.8	167.9	169.1

standard deviation	± 8.99	± 9.14	± 9.2

Reporting group values	Placebo followed by DKP/TRAM	Placebo followed by DKP	Placebo followed by TRAM
Number of subjects	54	53	54
Age categorical Units: Subjects			
From 18 to 80 years	54	53	54
Age continuous Units: years			
geometric mean	63.9	61	59.8
standard deviation	± 9	± 11.1	± 11.3
Gender categorical Units: Subjects			
Female	37	33	24
Male	17	20	30
Race/Ethnicity, Customized Units: Subjects			
Asian	0	0	2
White	54	53	52
Region of Enrollment Units: Subjects			
Serbia	5	5	5
Taiwan	0	0	2
Czech Republic	2	4	3
Hungary	17	16	11
Spain	0	0	0
Poland	2	2	3
Ukraine	6	6	3
Lithuania	6	5	11
Germany	0	0	0
Latvia	16	15	16
Weight Units: kg			
arithmetic mean	82.4	81.7	82.1
standard deviation	± 15.91	± 13.77	± 15.27
Height Units: cm			
arithmetic mean	166.1	168	169.9
standard deviation	± 8.47	± 9.49	± 7.94

Reporting group values	Total		
Number of subjects	641		
Age categorical Units: Subjects			
From 18 to 80 years	641		
Age continuous Units: years			
geometric mean			

standard deviation	-		

Gender categorical Units: Subjects			
Female	346		
Male	295		
Race/Ethnicity, Customized Units: Subjects			
Asian	7		
White	634		
Region of Enrollment Units: Subjects			
Serbia	62		
Taiwan	7		
Czech Republic	36		
Hungary	204		
Spain	2		
Poland	33		
Ukraine	56		
Lithuania	84		
Germany	4		
Latvia	153		
Weight Units: kg arithmetic mean standard deviation	- -		
Height Units: cm arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Screening

Reporting group description:

Screening period, for study eligibility assessment (within 4 weeks prior to randomization).
746 patients were screened and 105 of them were screening failure.

Reporting group title	DKP/TRAM followed by DKP/TRAM

Reporting group description:

Single-dose phase: Patients received DKP.TRIS 25mg + TRAM.HCl 75mg.
Single-dose treatment had to be administered on day 1.

Multiple-dose phase: Patients received DKP.TRIS 25mg + TRAM.HCl 75mg.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations (every 8 hours).

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Reporting group title	DKP followed by DKP

Reporting group description:

Single-dose phase: Patients received DKP.TRIS 25mg.
Single dose treatment had to be administered on day 1.

Multiple-dose phase: Patients received DKP.TRIS 25mg.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations (every 8 hours).

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Reporting group title	TRAM followed by TRAM

Reporting group description:

Single-dose phase: Patients received TRAM.HCl 100mg.
Single-dose treatment had to be administered on day 1.

Multiple-dose phase: Patients received TRAM.HCl 100mg.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations (every 8 hours).

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Reporting group title	Placebo followed by DKP/TRAM

Reporting group description:

Single-dose phase: Patients received Placebo (as one tablet matching DKP.TRIS 25mg + TRAM.HCl 75mg and matching DKP.TRIS 25mg and as two capsules matching TRAM.HCl 50mg).

Multiple-dose phase: Placebo assigned patients were allocated to receive DKP.TRIS 25mg + TRAM.HCl 75mg, every 8 hours.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations.

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Reporting group title	Placebo followed by DKP

Reporting group description:

Single-dose phase: Patients received Placebo (as one tablet matching DKP.TRIS 25mg + TRAM.HCl 75mg and matching DKP.TRIS 25mg and as two capsules matching TRAM.HCl 50mg).

Multiple-dose phase: Placebo assigned patients were allocated to receive DKP.TRIS 25mg, every 8 hours.
Multiple-dose treatment had to be orally administered (starting 8 hours after single dose phase) up to the morning of day 5, for a total of 12 drug administrations.

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Reporting group title	Placebo followed by TRAM

Reporting group description:

Single-dose phase: Patients received Placebo (as one tablet matching DKP.TRIS 25mg + TRAM.HCl 75mg and matching DKP.TRIS 25mg and as two capsules matching TRAM.HCl).

Multiple-dose phase: Placebo assigned patients were allocated to receive two capsules of TRAM.HCl 50mg, every 8 hours.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations.

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Reporting group title	End of study visit

Reporting group description:

Treatment blinidng was kept for the entire study duration un to the closure of database performed after the last patient last visit.

Subject analysis set title	DKP/TRAM
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Drug: Dexketoprofen/Tramadol single oral dose (first 8 hours); Arm type: experimental

Subject analysis set title	DEXKETOPROFEN
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Drug: Dexketoprofen single oral dose (first 8 hours); Arm type: active comparator;

Subject analysis set title	TRAMADOL
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Drug: Tramadol single oral dose (first 8 hours) Arm type: active comparator

Subject analysis set title	PLACEBO
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Drug: Placebo single oral dose (first 8 hours); Arm type: Placebo comparator

Subject analysis set title	DKP/TRAM
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Drug: Dexketoprofen/ Tramadol multiple doses; Arm type: experimental; Dexketoprofen/Tramadol multiple oral doses t.i.d. for 5 days (a total of 12 doses).
This subject analysis set include patients who took DKP/TRAM at single dose phase plus 1/3 of patients who took Placebo at single dose phase.

Subject analysis set title	DEXKETOPROFEN
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Drug: Dexketoprofen multiple doses; Arm type: active comparator; Dexketoprofen multiple oral doses t.i.d. for 5 days (a total of 12 doses).
This subject analysis set include patients who took dexketoprofen at single dose phase plus 1/3 of patients who took Placebo at single dose phase.

Subject analysis set title	TRAMADOL
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Drug: Tramadol multiple doses; Arm type: active comparator; Tramadol multiple oral doses t.i.d. for 5 days (a total of 12 doses).
This subject analysis set include patients who took tramadol at single dose phase plus 1/3 of patients who took Placebo at single dose phase.

Primary: SPID8 (Sum of Pain Intensity Differences Over 8 Hours)

End point title	SPID8 (Sum of Pain Intensity Differences Over 8 Hours)

End point description:

Sum of Pain Intensity Differences calculated as the weighted sum of the PI-VAS differences over 8 hours period. PI-VAS corresponds to the pain intensity measured by a 0-100 visual analogue scale (0= no pain to 100=worst pain imaginable) which was measured at 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h and 8h after the first dose. A higher value in SPID indicates greater pain relief.

The analysis was performed combining all randomization arms including placebo into one group, which resulted in the following 4 analysis groups: DKP/TRAM, DEXKETOPROFEN, TRAMADOL and Placebo.

End point type	Primary

End point timeframe:

over 8 hours after the first dose

End point values	DKP/TRAM	DEXKETOPROFEN	TRAMADOL	PLACEBO
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	159	161	160	161
Units: units on a scale				
arithmetic mean (standard deviation)	246.9 (± 156.5)	208.8 (± 154.69)	204.6 (± 145.79)	151.1 (± 158.51)

Statistical analyses

Statistical analysis title	SPID8 at rest (DKP.TRIS + TRAM.HCl vs. DKP.TRIS)

Statistical analysis description:

The null hypothesis of equality between DKP.TRIS + TRAM.HCl and DKP.TRIS and between DKP.TRIS + TRAM.HCl and TRAM.HCl was tested as co-primary efficacy endpoints using an analysis of covariance and a 2-sided overall significance of 5%. The two variables included as covariates in the ANCOVA model were treatment (as the main effect) and PI-level during screening.

Comparison groups	DKP/TRAM v DEXKETOPROFEN
Number of subjects included in analysis	320
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	standard error
Confidence interval	
level	95 %
sides	2-sided

Notes:

[1] - For all statistical analysis performed on data collected during the single-dose phase, the following treatment comparisons were presented:
DKP.TRIS + TRAM.HCl vs. DKP.TRIS
DKP.TRIS + TRAM.HCl vs. TRAM.HCl
TRAM.HCl vs. Placebo

Statistical analysis title	SPID8 at rest (DKP.TRIS + TRAM.HCl vs. TRAM.HCl)

Statistical analysis description:

The null hypothesis of equality between DKP.TRIS + TRAM.HCl and DKP.TRIS and between DKP.TRIS + TRAM.HCl and TRAM.HCl was tested as co-primary efficacy endpoints using an analysis of covariance and a 2-sided overall significance of 5%. The two variables included as covariates in the ANCOVA model were treatment (as the main effect) and PI-level during screening.

Comparison groups	DKP/TRAM v TRAMADOL
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	standard error
Confidence interval	
level	95 %
sides	2-sided

Notes:

[2] - For all statistical analysis performed on data collected during the single-dose phase, the following treatment comparisons were presented:
DKP.TRIS + TRAM.HCl vs. DKP.TRIS
DKP.TRIS + TRAM.HCl vs. TRAM.HCl
TRAM.HCl vs. Placebo
DKP.TRIS vs. Placebo

Statistical analysis title	SPID8 at rest (TRAM.HCl vs. Placebo)

Statistical analysis description:

The null hypothesis of equality between DKP.TRIS + TRAM.HCl and DKP.TRIS and between DKP.TRIS + TRAM.HCl and TRAM.HCl was tested as co-primary efficacy endpoints using an analysis of covariance and a 2-sided overall significance of 5%. The two variables included as covariates in the ANCOVA model were treatment (as the main effect) and PI-level during screening.

Comparison groups	PLACEBO v TRAMADOL
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	standard error
Confidence interval	
level	95 %
sides	2-sided

Notes:

[3] - For all statistical analysis performed on data collected during the single-dose phase, the following treatment comparisons were presented:
DKP.TRIS + TRAM.HCl vs. DKP.TRIS
DKP.TRIS + TRAM.HCl vs. TRAM.HCl
TRAM.HCl vs. Placebo
DKP.TRIS vs. Placebo

Statistical analysis title	SPID8 at rest (DKP.TRIS + Placebo)

Statistical analysis description:

The null hypothesis of equality between DKP.TRIS + TRAM.HCl and DKP.TRIS and between DKP.TRIS + TRAM.HCl and TRAM.HCl was tested as co-primary efficacy endpoints using an analysis of covariance and a 2-sided overall significance of 5%. The two variables included as covariates in the ANCOVA model were treatment (as the main effect) and PI-level during screening.

Comparison groups	DEXKETOPROFEN v PLACEBO
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	standard error
Confidence interval	
level	95 %
sides	2-sided

Notes:

[4] - For all statistical analysis performed on data collected during the single-dose phase, the following treatment comparisons were presented:
DKP.TRIS + TRAM.HCl vs. DKP.TRIS
DKP.TRIS + TRAM.HCl vs. TRAM.HCl
TRAM.HCl vs. Placebo
DKP.TRIS vs. Placebo

Secondary: SPID48 (Sum of Pain Intensity Differences Over 48 Hours of the Multiple-dose Phase)

End point title	SPID48 (Sum of Pain Intensity Differences Over 48 Hours of the Multiple-dose Phase)

End point description:

Sum of Pain Intensity Differences calculated as the weighted sum of the PI-VAS differences over 48 hours of the multiple-dose phase.

PI-VAS corresponds to the pain intensity measured by a 0-100 visual analogue scale (0=no pain to 100 worst pain imaginable) which was measured every two hours over the first 48 hours of the multiple-dose phase. A higher value in SPID indicates greater pain relief.

The analysis was performed combining all randomization arms including the same active treatment, which resulted in the following 3 analysis groups: DKP/TRAM, DEXKETOPROFEN and TRAMADOL.

End point type	Secondary

End point timeframe:

over 48 hours of the multiple-dose phase

End point values	DKP/TRAM	DEXKETOPROFEN	TRAMADOL	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	213	214	214	
Units: units on a scale				
arithmetic mean (standard deviation)	1943.7 (± 1000.51)	1677.5 (± 1070.91)	1765.6 (± 963.49)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Responders According to PI-VAS (Pain Intensity - Visual Analogue Scale)

End point title	Percentage of Responders According to PI-VAS (Pain Intensity -

	Visual Analogue Scale)

End point description:

Percentage of responders; response defined as achievement a mean pain intensity, PI-VAS 40 mm (PI-VAS corresponds to the pain intensity measured by a 0-100 visual analogue scale, 0=no pain to 100=worst pain imaginable), over 48 hours of the multiple-dose phase.

The analysis was performed combining all randomization arms including the same active treatment, which resulted in the following 3 analysis groups: DKP/TRAM, DEXKETOPROFEN and TRAMADOL.

End point type	Secondary

End point timeframe:

over 48 hours of the multiple-dose phase

End point values	DKP/TRAM	DEXKETOPROFEN	TRAMADOL	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	213	214	214	
Units: percentage of participants				
number (not applicable)	90.1	76.6	82.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Responders According to 50% Max TOTPAR (Total Pain Relief)

End point title	Percentage of Responders According to 50% Max TOTPAR (Total Pain Relief)

End point description:

Percentage of responders over 8 hours after first dose, according to the 50% maximum total pain relief rule: maximum TOTPAR calculated as the theoretical maximum weighted sum of PAR-VRS (Pain Relief - Verbal Rating Scale: pain relief 0=none, 4=complete) scores.

The analysis was performed combining all randomization arms including placebo into one group, which resulted in the following 4 analysis groups: DKP/TRAM, DEXKETOPROFEN, TRAMADOL and Placebo.

End point type	Secondary

End point timeframe:

over 8 hours after the first dose

End point values	DKP/TRAM	DEXKETOPROFEN	TRAMADOL	PLACEBO
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	159	161	160	161
Units: percentage of participants				
number (not applicable)	57.9	56.5	51.9	37.9

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Study duration for patients was up to 6 weeks.

Adverse event reporting additional description:

Analyzed for the Safety population (all randomized patients who received at least one dose of the study treatment). Includes adverse events emerging after at least one dose of active study treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	DKP/TRAM Followed by DKP/TRAM

Reporting group description:

Single-dose phase: Patients received DKP.TRIS 25mg + TRAM.HCl 75mg.
Single-dose treatment had to be administered on day 1.

Multiple-dose phase: Patients received DKP.TRIS 25mg + TRAM.HCl 75mg.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations (every 8 hours).

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Reporting group title	DKP Followed by DKP

Reporting group description:

Single-dose phase: Patients received DKP.TRIS 25mg.
Single dose treatment had to be administered on day 1.

Multiple-dose phase: Patients received DKP.TRIS 25mg.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations (every 8 hours).

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy deisgn) had to be orally administered, together with approximately 150 ml of still/tap water.

Reporting group title	TRAM Followed by TRAM

Reporting group description:

Single-dose phase: Patients received TRAM.HCl 100mg.
Single-dose treatment had to be administered on day 1.

Multiple-dose phase: Patients received TRAM.HCl 100mg.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations (every 8 hours).

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Reporting group title	Placebo Followed by DKP/TRAM

Reporting group description:

Single-dose phase: Patients received Placebo (as one tablet matching DKP.TRIS 25mg + TRAM.HCl 75mg and matching DKP.TRIS 25mg and as two capsules matching TRAM.HCl 50mg).

Multiple-dose phase: Placebo assigned patients were allocated to receive DKP.TRIS 25mg + TRAM.HCl 75mg, every 8 hours.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations.

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Reporting group title	Placebo Followed by DKP

Reporting group description:

Single-dose phase: Patients received Placebo (as one tablet matching DKP.TRIS 25mg + TRAM.HCl 75mg and matching DKP.TRIS 25mg and as two capsules matching TRAM.HCl 50mg).

Multiple-dose phase: Placebo assigned patients were allocated to receive DKP.TRIS 25mg, every 8 hours.
Multiple-dose treatment had to be orally administered (starting 8 hours after single dose phase) up to the morning of day 5, for a total of 12 drug administrations.

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Reporting group title	Placebo Followed by TRAM

Reporting group description:

Single-dose phase: Patients received Placebo (as one tablet matching DKP.TRIS 25mg + TRAM.HCl 75mg and matching DKP.TRIS 25mg and as two capsules matching TRAM.HCl).

Multiple-dose phase: Placebo assigned patients were allocated to receive two capsules of TRAM.HCl 50mg, every 8 hours.
Multiple-dose treatment had to be orally administered (starting 8 hours after the single dose phase) up to the morning of day 5, for a total of 12 drug administrations.

Each dose treatment consisting of 1 film-coated tablet and 2 capsules (according to double dummy design) had to be orally administered, together with approximately 150 ml of still/tap water.

Serious adverse events	DKP/TRAM Followed by DKP/TRAM	DKP Followed by DKP	TRAM Followed by TRAM
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 159 (1.26%)	3 / 161 (1.86%)	1 / 160 (0.63%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Periprosthetic fracture			
subjects affected / exposed	0 / 159 (0.00%)	1 / 161 (0.62%)	0 / 160 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac Disorder			
subjects affected / exposed	1 / 159 (0.63%)	0 / 161 (0.00%)	0 / 160 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Bone operation			
subjects affected / exposed	0 / 159 (0.00%)	1 / 161 (0.62%)	1 / 160 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart valve replacement			

subjects affected / exposed	1 / 159 (0.63%)	0 / 161 (0.00%)	0 / 160 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular graft			
subjects affected / exposed	1 / 159 (0.63%)	0 / 161 (0.00%)	0 / 160 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Device dislocation			
subjects affected / exposed	0 / 159 (0.00%)	0 / 161 (0.00%)	1 / 160 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face oedema			
subjects affected / exposed	1 / 159 (0.63%)	0 / 161 (0.00%)	0 / 160 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Periorbital oedema			
subjects affected / exposed	1 / 159 (0.63%)	0 / 161 (0.00%)	0 / 160 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	0 / 159 (0.00%)	1 / 161 (0.62%)	0 / 160 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Laryngeal oedema			
subjects affected / exposed	1 / 159 (0.63%)	0 / 161 (0.00%)	0 / 160 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 159 (0.00%)	1 / 161 (0.62%)	0 / 160 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 159 (0.63%)	0 / 161 (0.00%)	0 / 160 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Soft tissue infection			
subjects affected / exposed	0 / 159 (0.00%)	0 / 161 (0.00%)	0 / 160 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo Followed by DKP/TRAM	Placebo Followed by DKP	Placebo Followed by TRAM
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	0 / 54 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Periprosthetic fracture			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac Disorder			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Bone operation			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart valve replacement			

subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular graft			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Device dislocation			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face oedema			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Periorbital oedema			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Laryngeal oedema			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 54 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Soft tissue infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	DKP/TRAM Followed by DKP/TRAM	DKP Followed by DKP	TRAM Followed by TRAM
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 159 (9.43%)	18 / 161 (11.18%)	24 / 160 (15.00%)
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	7 / 159 (4.40%)	6 / 161 (3.73%)	5 / 160 (3.13%)
occurrences (all)	7	6	5
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 159 (1.89%)	1 / 161 (0.62%)	1 / 160 (0.63%)
occurrences (all)	3	1	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 159 (1.89%)	9 / 161 (5.59%)	11 / 160 (6.88%)
occurrences (all)	3	10	12
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 159 (1.26%)	4 / 161 (2.48%)	9 / 160 (5.63%)
occurrences (all)	2	4	9

Non-serious adverse events	Placebo Followed by DKP/TRAM	Placebo Followed by DKP	Placebo Followed by TRAM
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 54 (16.67%)	2 / 53 (3.77%)	5 / 54 (9.26%)
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	3 / 54 (5.56%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences (all)	3	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 54 (5.56%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences (all)	3	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 54 (5.56%)	2 / 53 (3.77%)	4 / 54 (7.41%)
occurrences (all)	3	3	5
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2013	The content of this Amendment Nº 1 refers to changes to the study protocol version 1.0 of 07 December 2012. This amendment does not alter the scientific or medical basis of the protocol. An integrated version of study protocol, inclusive of the current Amendment N° 1 was issued in order to have a single updated study protocol document available for the investigator and identified as the study protocol version 2.0 of 15 October 2013.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported