



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 following abdominal hysterectomy

Summary

EudraCT number	2012-004545-32
Trial protocol	SK HU ES LV PL LT RO
Global end of trial date	19 May 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-04
-----------------------	------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01904149
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	Cl. Research Corporate Director, Menarini Ricerche S.p.A., +39 05556809933, ACapriati@menarini-ricerche.it
Scientific contact	Cl. 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	01 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 May 2014
Global end of trial reached?	Yes
Global end of trial date	19 May 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 total/subtotal abdominal hysterectomy.

Protection of trial subjects:

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

For patients participating in the study, Menarini Ricerche S.p.A. stipulated an insurance policy in accordance with local regulatory requirements. Details on the insurance company, the insurance number and conditions were 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 was expected to provide adequate pain relief for the participating patients without raising any safety concerns. Patients were hospitalized for the entire study treatment duration and monitoring of AEs were conducted during this period. Upon discharge, patients were instructed to contact the site immediately in case of any medical emergency.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 May 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	Poland: 234
Country: Number of subjects enrolled	Romania: 138
Country: Number of subjects enrolled	Slovakia: 39
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Hungary: 89
Country: Number of subjects enrolled	Latvia: 72
Country: Number of subjects enrolled	Lithuania: 14
Country: Number of subjects enrolled	Russian Federation: 15

Worldwide total number of subjects	606
EEA total number of subjects	591

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)	592
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was screened on 29 May 2013 and the first patient randomized was on 04 June 2013. The last patient completed the study on 19 May 2014. The study was conducted on 38 study centres in 9 countries (Hungary, Latvia, Lithuania, Poland, Romania, Russia, Slovakia, Spain and Ukraine).

Pre-assignment

Screening details:

A total of 677 patients were screened and 606 of them were randomized (screening failure rate was 10.5%). 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). A total of 677 patients were screened and 71 patients were excluded as screening failure.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Screening
Started	606
Completed	606

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 administered up to the morning of day 3, for a total of 6 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 150ml 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 150mg 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 administered up to the morning of day 3, for a total of 6 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 150ml 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 150ml of still/tap water.

Arm title	TRAM followed by TRAM
------------------	-----------------------

Arm description:

Single-dose phase: Patients received TRAM.HCl 75mg.

Single-dose treatment had to be administered on day 1.

Multiple-dose phase: Patients received TRAM.HCl 75mg.

Multiple-dose treatment had to be administered up to the morning of day 3, for a total of 6 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 150ml 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 (as 2 capsules Contramal 50mg)	
Treatment had to be orally administered, together with approximately 150ml 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 administered up to the morning of day 3, for a total of 6 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 150ml 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 150ml 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 administered up to the morning of day 3, for a total of 6 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 150ml 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 150ml 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:
DKP.TRIS 25mg
Treatment had to be orally administered, together with approximately 150ml 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 50mg).

Multiple-dose phase: Placebo assigned patients were allocated to receive TRAM.HCl 75mg, every 8 hours.

Multiple-dose treatment had to be administered up to the morning of day 3, for a total of 6 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 150ml 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 150ml 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:
TRAM.HCl 100mg (as two capsules Contramal 50mg).
Treatment had to be orally administered, together with approximately 150ml 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 baseline, 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	152	151	150
Completed	147	140	148
Not completed	5	11	2
Consent withdrawn by subject	1	3	1
Adverse event, non-fatal	3	4	-
Non-compliance with study drug	1	-	-
Lack of efficacy	-	3	1

Protocol deviation	-	1	-
--------------------	---	---	---

Number of subjects in period 2	Placebo followed by DKP/TRAM	Placebo followed by DKP	Placebo followed by TRAM
Started	51	51	51
Completed	47	46	48
Not completed	4	5	3
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	1	1	2
Non-compliance with study drug	-	-	-
Lack of efficacy	3	3	1
Protocol deviation	-	-	-

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:	
End of study visit, for final safety follow-up (1 week after last dose intake).	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	End of study visit
Started	576
Completed	576

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 administered up to the morning of day 3, for a total of 6 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 150ml 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 administered up to the morning of day 3, for a total of 6 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 150ml of still/tap water.

Reporting group title	TRAM followed by TRAM
-----------------------	-----------------------

Reporting group description:

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

Multiple-dose phase: Patients received TRAM.HCl 75mg.
Multiple-dose treatment had to be administered up to the morning of day 3, for a total of 6 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 150ml 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 administered up to the morning of day 3, for a total of 6 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 150ml 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 administered up to the morning of day 3, for a total of 6 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 150ml 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 50mg).	
Multiple-dose phase: Placebo assigned patients were allocated to receive TRAM.HCl 75mg, every 8 hours.	
Multiple-dose treatment had to be administered up to the morning of day 3, for a total of 6 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 150ml of still/tap water.	

Reporting group values	DKP/TRAM followed by DKP/TRAM	DKP followed by DKP	TRAM followed by TRAM
Number of subjects	152	151	150
Age categorical			
Units: Subjects			
From 18 to 75 years	152	151	150
Age continuous			
From 18 to 75 years old			
Units: years			
arithmetic mean	48.1	47.2	47.6
standard deviation	± 6.7	± 7.07	± 6.87
Gender categorical			
Units: Subjects			
Female	152	151	150
Race/Ethnicity, Customized			
Units: Subjects			
Race/Ethnicity, Customized	152	151	150
Region of Enrollment			
Units: Subjects			
Hungary	22	19	26
Slovakia	7	13	8
Spain	1	2	1
Poland	63	53	60
Romania	32	40	32
Lithuania	2	4	3
Russian Federation	3	3	3
Latvia	22	17	17
Weight			
Units: Kg			
arithmetic mean	75.2	72.1	71.3
standard deviation	± 15.15	± 13.54	± 12.17
Height			
Units: cm			
arithmetic mean	163.9	163.7	164.1
standard deviation	± 5.4	± 6.37	± 6.1

Reporting group values	Placebo followed by DKP/TRAM	Placebo followed by DKP	Placebo followed by TRAM
Number of subjects	51	51	51

Age categorical			
Units: Subjects			
From 18 to 75 years	51	51	51
Age continuous			
From 18 to 75 years old			
Units: years			
arithmetic mean	47.4	47.4	47.2
standard deviation	± 6.82	± 7.46	± 4.6
Gender categorical			
Units: Subjects			
Female	51	51	51
Race/Ethnicity, Customized			
Units: Subjects			
Race/Ethnicity, Customized	51	51	51
Region of Enrollment			
Units: Subjects			
Hungary	8	7	7
Slovakia	5	2	4
Spain	0	0	1
Poland	18	23	17
Romania	10	12	12
Lithuania	1	1	3
Russian Federation	2	2	2
Latvia	7	4	5
Weight			
Units: Kg			
arithmetic mean	73.6	72.9	72.6
standard deviation	± 13.74	± 14.6	± 10.97
Height			
Units: cm			
arithmetic mean	164.5	163.5	164.4
standard deviation	± 6.17	± 5.94	± 5.59

Reporting group values	Total		
Number of subjects	606		
Age categorical			
Units: Subjects			
From 18 to 75 years	606		
Age continuous			
From 18 to 75 years old			
Units: years			
arithmetic mean	-		
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	606		
Race/Ethnicity, Customized			
Units: Subjects			
Race/Ethnicity, Customized	606		
Region of Enrollment			
Units: Subjects			

Hungary	89		
Slovakia	39		
Spain	5		
Poland	234		
Romania	138		
Lithuania	14		
Russian Federation	15		
Latvia	72		
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).
A total of 677 patients were screened and 71 patients were excluded as 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 administered up to the morning of day 3, for a total of 6 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 150ml 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 administered up to the morning of day 3, for a total of 6 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 150ml of still/tap water.

Reporting group title	TRAM followed by TRAM
-----------------------	-----------------------

Reporting group description:

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

Multiple-dose phase: Patients received TRAM.HCl 75mg.
Multiple-dose treatment had to be administered up to the morning of day 3, for a total of 6 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 150ml 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 administered up to the morning of day 3, for a total of 6 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 150ml 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 administered up to the morning of day 3, for a total of 6 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 150ml 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 50mg).

Multiple-dose phase: Placebo assigned patients were allocated to receive TRAM.HCl 75mg, every 8 hours.

Multiple-dose treatment had to be administered up to the morning of day 3, for a total of 6 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 150ml of still/tap water.

Reporting group title	End of study visit
-----------------------	--------------------

Reporting group description:

End of study visit, for final safety follow-up (1 week after last dose intake).

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, Dexketoprofen/Tramadol single oral dose (first 8 hours)

Subject analysis set title	DESKETOPROFEN
----------------------------	---------------

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

Subject analysis set description:

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

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; Tramadol single oral dose (first 8 hours).

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; Placebo single oral dose (first 8 hours).

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 3 days (a total of 6 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	DESKETOPROFEN
----------------------------	---------------

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 3 days (a total of 6 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 3 days (a total of 6 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, 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	152	151	150	153
Units: units on a scale				
arithmetic mean (standard deviation)	241.8 (± 139.06)	184.5 (± 139.23)	157.3 (± 150.89)	117 (± 121.8)

Statistical analyses

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

Statistical analysis description:

The null hypothesis of equality between DKP.TRIS + TRAM.HCI and DKP.TRIS and between DKP.TRIS + TRAM.HCI and TRAM.HCI 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	303
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.HCI vs. DKP.TRIS

DKP.TRIS + TRAM.HCI vs. TRAM.HCI

TRAM.HCI vs. Placebo

DKP.TRIS 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	TRAMADOL v DKP/TRAM
Number of subjects included in analysis	302
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	TRAMADOL v PLACEBO
Number of subjects included in analysis	303
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	PLACEBO v DEXKETOPROFEN
Number of subjects included in analysis	304
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.HCI vs. DKP.TRIS

DKP.TRIS + TRAM.HCI vs. TRAM.HCI

TRAM.HCI vs. Placebo

DKP.TRIS vs. Placebo

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 the 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	152	151	150	153
Units: percentage of participants				
number (not applicable)	65.8	47.7	44	30.7

Statistical analyses

No statistical analyses for this end point

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	203	202	201	
Units: units on a scale				
arithmetic mean (standard deviation)	2273 (± 864.03)	1965.2 (± 912.19)	2035 (± 919.49)	

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	203	202	201	
Units: percentage of participants				
number (not applicable)	94.1	82.7	88.6	

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 patients randomized 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 administered up to the morning of day 3, for a total of 6 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 150ml 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 administered up to the morning of day 3, for a total of 6 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 150ml of still/tap water.

Reporting group title	TRAM followed by TRAM
-----------------------	-----------------------

Reporting group description:

Single-dose phase: Patients received TRAM.HCl 75mg.

Single-dose treatment had to be administered on day 1.

Multiple-dose phase: Patients received TRAM.HCl 75mg.

Multiple-dose treatment had to be administered up to the morning of day 3, for a total of 6 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 150ml 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 administered up to the morning of day 3, for a total of 6 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 150ml 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 administered up to the morning of day 3, for a total of 6 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 150ml 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 50mg).

Multiple-dose phase: Placebo assigned patients were allocated to receive TRAM.HCl 75mg, every 8 hours.

Multiple-dose treatment had to be administered up to the morning of day 3, for a total of 6 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 150ml 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	7 / 151 (4.64%)	2 / 152 (1.32%)	1 / 150 (0.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	0 / 150 (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
Anaemia postoperative			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	0 / 150 (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
Post procedural haemorrhage			
subjects affected / exposed	1 / 151 (0.66%)	1 / 152 (0.66%)	0 / 150 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Laparotomy			

subjects affected / exposed	0 / 151 (0.00%)	0 / 152 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	0 / 150 (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
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	0 / 150 (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
Diarrhoea			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	0 / 150 (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
Peritoneal haematoma			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	0 / 150 (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
Reproductive system and breast disorders			
Endometrial cancer stage I			
subjects affected / exposed	0 / 151 (0.00%)	0 / 152 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
fallopian tube torsion			
subjects affected / exposed	0 / 151 (0.00%)	0 / 152 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ovarian torsion			

subjects affected / exposed	0 / 151 (0.00%)	0 / 152 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	0 / 150 (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			
Pneumonia			
subjects affected / exposed	1 / 151 (0.66%)	0 / 152 (0.00%)	0 / 150 (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
Postoperative wound infection			
subjects affected / exposed	0 / 151 (0.00%)	1 / 152 (0.66%)	0 / 150 (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

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	0 / 52 (0.00%)	0 / 50 (0.00%)	0 / 51 (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			
Abdominal wound dehiscence			
subjects affected / exposed	0 / 52 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Anaemia postoperative			
subjects affected / exposed	0 / 52 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Post procedural haemorrhage			

subjects affected / exposed	0 / 52 (0.00%)	0 / 50 (0.00%)	0 / 51 (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			
Laparotomy			
subjects affected / exposed	0 / 52 (0.00%)	0 / 50 (0.00%)	0 / 51 (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			
Pyrexia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 50 (0.00%)	0 / 51 (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			
Abdominal pain lower			
subjects affected / exposed	0 / 52 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Diarrhoea			
subjects affected / exposed	0 / 52 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Peritoneal haematoma			
subjects affected / exposed	0 / 52 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Reproductive system and breast disorders			
Endometrial cancer stage I			
subjects affected / exposed	0 / 52 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
fallopian tube torsion			

subjects affected / exposed	0 / 52 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
ovarian torsion			
subjects affected / exposed	0 / 52 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	0 / 52 (0.00%)	0 / 50 (0.00%)	0 / 51 (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			
Pneumonia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Postoperative wound infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 50 (0.00%)	0 / 51 (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

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	22 / 151 (14.57%)	22 / 152 (14.47%)	33 / 150 (22.00%)
Investigations			
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 151 (0.66%)	2 / 152 (1.32%)	2 / 150 (1.33%)
occurrences (all)	1	2	2
Platelet count increased			
subjects affected / exposed	3 / 151 (1.99%)	8 / 152 (5.26%)	9 / 150 (6.00%)
occurrences (all)	3	8	9

General disorders and administration site conditions			
Constipation			
subjects affected / exposed	6 / 151 (3.97%)	2 / 152 (1.32%)	6 / 150 (4.00%)
occurrences (all)	6	2	6
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 151 (5.96%)	6 / 152 (3.95%)	14 / 150 (9.33%)
occurrences (all)	10	7	15
Vomiting			
subjects affected / exposed	5 / 151 (3.31%)	6 / 152 (3.95%)	8 / 150 (5.33%)
occurrences (all)	5	6	8

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	3 / 52 (5.77%)	10 / 50 (20.00%)	10 / 51 (19.61%)
Investigations			
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 52 (0.00%)	3 / 50 (6.00%)	0 / 51 (0.00%)
occurrences (all)	0	3	0
Platelet count increased			
subjects affected / exposed	0 / 52 (0.00%)	3 / 50 (6.00%)	3 / 51 (5.88%)
occurrences (all)	0	3	3
General disorders and administration site conditions			
Constipation			
subjects affected / exposed	0 / 52 (0.00%)	2 / 50 (4.00%)	3 / 51 (5.88%)
occurrences (all)	0	2	3
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 52 (5.77%)	2 / 50 (4.00%)	5 / 51 (9.80%)
occurrences (all)	3	2	6
Vomiting			
subjects affected / exposed	0 / 52 (0.00%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 October 2013	<p>An integrated version of the study protocol, inclusive of the current Amendment N° 1, has been issued in order to have a single updated document available for the Investigator and it is identified as the study protocol version 2.0 of 15 October 2013.</p> <p>Based on the comments and recommendations received from the participating Investigators during the Investigator Meeting and the conduct of the study, some of the inclusion/exclusion criteria and study procedures have been changed and/or clarified. In addition, this amendment includes administrative changes.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported