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

Summary

EudraCT number	2015-004152-22
Trial protocol	GB HU ES PL IT
Global end of trial date	14 February 2017

Results information

Result version number	v1 (current)
This version publication date	27 October 2018
First version publication date	27 October 2018

Trial information

Trial identification

Sponsor protocol code	DEX-TRA-06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02777970
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. Sciences Corporate Director, Menarini Ricerche S.p.A., +39 0555680 9990, ACapriati@menarini-ricerche.it
Scientific contact	Cl. Sciences Corporate Director, Menarini Ricerche S.p.A., +39 0555680 9990, 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	04 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 February 2017
Global end of trial reached?	Yes
Global end of trial date	14 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

Rescue medication, namely Ibuprofen 400 mg, was available at any time during the post-dose period.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 April 2016
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	Italy: 180
Country: Number of subjects enrolled	Poland: 127
Country: Number of subjects enrolled	Spain: 141
Country: Number of subjects enrolled	United Kingdom: 139
Country: Number of subjects enrolled	Hungary: 67
Worldwide total number of subjects	654
EEA total number of subjects	654

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)	1
Adults (18-64 years)	653
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 18 sites across 5 European countries: Hungary, Italy, Poland, Spain and United Kingdom. The clinical phase of the study started on 28th April 2016 (first enrolled patient, randomised on 11h May) and concluded on 14th February 2017 (last patient out).
1 patient was excluded from all the analyses because <18 years old

Pre-assignment

Screening details:

Male or female patients, age> 18 years, experiencing moderate to severe pain (Numerical Rating Scale, NRS ≥4) within 4 hours after the end of surgery (under local anaesthesia) for extraction of at least one impacted lower third molar.
Screened 792, randomised 654. Main SF reason: pain<4 (49), incl/excl crit (31), other (45), withdrawal(13).

Period 1

Period 1 title	Screening period
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

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Screening
Started	653
Completed	653

Period 2

Period 2 title	Treatment/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:

Double dummy technique used for this study.

Arms

Are arms mutually exclusive?	Yes
Arm title	DKP.TRIS/TRAM.HCl

Arm description:

Dexketoprofen trometamol/Tramadol hydrochloride 25mg /75mg

Arm type	Experimental
Investigational medicinal product name	Dexketoprofen trometamol/Tramadol hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Single dose of dexketoprofen trometamol/Tramadol hydrochloride 25mg /75mg fixed dose combination oral tablet plus 2 tablets of placebo matching the active comparator

Arm title	TRAM.HCl/ Paracetamol

Arm description:

Tramadol hydrochloride/ Paracetamol 75mg/650mg

Arm type	Active comparator
Investigational medicinal product name	Tramadol / Paracetamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Single dose of tramadol hydrochloride / paracetamol 75mg/650mg as 2 x [37.5 mg/325 mg] fixed dose combination oral tablets plus 1 tablet of placebo matching DKP.TRIS/TRAM.HCl

Arm title	Placebo

Arm description:

Placebo matching DKP.TRIS/TRAM.HCl and TRAM.HCl/Paracetamol

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Single dose of 1 tablet placebo matching DKP.TRIS/TRAM.HCl 25/75 mg plus 2 tablets placebo matching TRAM.HCl/Paracetamol 37.5/325 mg

Notes:

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

Justification: period 2 is the baseline period since the pain intensity assessed at T0, after the randomization, immediately prior to the administration of the study treatment, was considered as baseline pain intensity.

Number of subjects in period 2[2]	DKP.TRIS/TRAM.HCl	TRAM.HCl/ Paracetamol	Placebo
Started	260	262	131
Completed	260	262	131

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: one patient was excluded from all the analyses because underage

Baseline characteristics

Reporting groups	
Reporting group title	DKP.TRIS/TRAM.HCl
Reporting group description:	
Dexketoprofen trometamol/Tramadol hydrochloride 25mg /75mg	
Reporting group title	TRAM.HCl/ Paracetamol
Reporting group description:	
Tramadol hydrochloride/ Paracetamol 75mg/650mg	
Reporting group title	Placebo
Reporting group description:	
Placebo matching DKP.TRIS/TRAM.HCl and TRAM.HCl/Paracetamol	

Reporting group values	DKP.TRIS/TRAM.HCl	TRAM.HCl/ Paracetamol	Placebo
Number of subjects	260	262	131
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	260	262	131
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Mean Age at the Informed Consent signature date			
Units: years			
arithmetic mean	26.8	27.1	26.5
standard deviation	± 7.48	± 8.13	± 7.67
Gender categorical			
Male and females patients could be enrolled, no rule adopted.			
Units: Subjects			
Female	152	158	78
Male	108	104	53
Pain Intensity at Qualification			
Descriptive Statistics of Pain Intensity scores at Qualification (namely within 4 hours after the end of the surgery) measured on a Numerical Rating Scale (NRS) from 0 to 10			
Units: point			
arithmetic mean	5	4.9	4.8
standard deviation	± 1.19	± 1.12	± 1.1
Pain Intensity at T-0h (baseline)			
Descriptive statistics of Pain Intensity at T-oh (baseline defined as NRS-PI assessed immediately prior to drug administration) measured on a NRS from 0 to 10			
Units: point			
arithmetic mean	5.7	5.5	5.6
standard deviation	± 1.36	± 1.34	± 1.3

Reporting group values	Total		
Number of subjects	653		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	653		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Mean Age at the Informed Consent signature date			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Male and females patients could be enrolled, no rule adopted.			
Units: Subjects			
Female	388		
Male	265		
Pain Intensity at Qualification			
Descriptive Statistics of Pain Intensity scores at Qualification (namely within 4 hours after the end of the surgery) measured on a Numerical Rating Scale (NRS) from 0 to 10			
Units: point			
arithmetic mean			
standard deviation	-		
Pain Intensity at T-0h (baseline)			
Descriptive statistics of Pain Intensity at T-oh (baseline defined as NRS-PI assessed immediately prior to drug administration) measured on a NRS from 0 to 10			
Units: point			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients randomised. Note: 1 patient was excluded because underage	
Subject analysis set title	PP population
Subject analysis set type	Per protocol
Subject analysis set description: All patients of the ITT population who did not experience relevant protocol violations related to the efficacy endpoint of primary interest.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who have received at least one dose of the study treatment.
Note: 1 patient was excluded because underage

Reporting group values	ITT population	PP population	Safety population
Number of subjects	653	620	653
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	653	620	653
From 65-84 years			
85 years and over			
Age continuous			
Mean Age at the Informed Consent signature date			
Units: years			
arithmetic mean	26.9	26.9	26.9
standard deviation	± 7.78	± 7.85	± 7.78
Gender categorical			
Male and females patients could be enrolled, no rule adopted.			
Units: Subjects			
Female	388	369	388
Male	265	251	265
Pain Intensity at Qualification			
Descriptive Statistics of Pain Intensity scores at Qualification (namely within 4 hours after the end of the surgery) measured on a Numerical Rating Scale (NRS) from 0 to 10			
Units: point			
arithmetic mean	4.9	4.9	4.9
standard deviation	± 1.14	± 1.15	± 1.14
Pain Intensity at T-0h (baseline)			
Descriptive statistics of Pain Intensity at T-oh (baseline defined as NRS-PI assessed immediately prior to drug administration) measured on a NRS from 0 to 10			
Units: point			
arithmetic mean	5.6	5.6	5.6
standard deviation	± 1.34	± 1.33	± 1.34

End points

End points reporting groups

Reporting group title	Screening
Reporting group description:	
Screening period for study eligibility assessment	
Reporting group title	DKP.TRIS/TRAM.HCl
Reporting group description:	
Dexketoprofen trometamol/Tramadol hydrochloride 25mg /75mg	
Reporting group title	TRAM.HCl/ Paracetamol
Reporting group description:	
Tramadol hydrochloride/ Paracetamol 75mg/650mg	
Reporting group title	Placebo
Reporting group description:	
Placebo matching DKP.TRIS/TRAM.HCl and TRAM.HCl/Paracetamol	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients randomised. Note: 1 patient was excluded because underage	
Subject analysis set title	PP population
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients of the ITT population who did not experience relevant protocol violations related to the efficacy endpoint of primary interest.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who have received at least one dose of the study treatment. Note: 1 patient was excluded because underage	

Primary: Total pain relief (TOTPAR6)

End point title	Total pain relief (TOTPAR6)
End point description:	
The primary endpoint of the study was the total pain relief over 6 hours post-dose period (TOTPAR6).	
End point type	Primary
End point timeframe:	
over 6-hour post dose period	

End point values	DKP.TRIS/TRAM.HCl	TRAM.HCl/ Paracetamol	Placebo	ITT population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	260	262	131	653
Units: point				
arithmetic mean (standard deviation)	13 (± 6.97)	9.2 (± 7.65)	1.9 (± 3.89)	9.2 (± 7.88)

Statistical analyses

Statistical analysis title	Primary Efficacy end-point
Comparison groups	TRAM.HCl/ Paracetamol v DKP.TRIS/TRAM.HCl
Number of subjects included in analysis	522
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.025
Method	ANCOVA

Notes:

[1] - The hypothesis of non-inferiority of DKP.TRIS/TRAM.HCl versus TRAM.HCl/Paracetamol was tested for both ITT and PP population by using an ANCOVA model with treatment (as main effect) and baseline PI (NRS) as covariate. 20% was set as non-inferiority limit.

Statistical analysis title	Primary efficacy endpoint
Comparison groups	DKP.TRIS/TRAM.HCl v TRAM.HCl/ Paracetamol
Number of subjects included in analysis	522
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Primary: Total pain relief (TOTPAR6)

End point title	Total pain relief (TOTPAR6)

End point description:

The primary endpoint of the study was the total pain relief over 6 hours post-dose period (TOTPAR6).

End point type	Primary

End point timeframe:

over 6-hour post-dose

End point values	DKP.TRIS/TRAM.HCl	TRAM.HCl/ Paracetamol	Placebo	PP population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	246	248	126	620
Units: point				
arithmetic mean (standard deviation)	12.9 (± 6.89)	9.2 (± 7.71)	1.9 (± 3.9)	9.2 (± 7.88)

Statistical analyses

Statistical analysis title	Primary Efficacy end-point
Comparison groups	DKP.TRIS/TRAM.HCl v TRAM.HCl/ Paracetamol

Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.025
Method	ANCOVA

Notes:

[2] - The hypothesis of non-inferiority of DKP.TRIS/TRAM.HCl versus TRAM.HCl/Paracetamol was tested for both ITT and PP population by using an ANCOVA model with treatment (as main effect) and baseline PI (NRS) as covariate. 20% was set as non-inferiority limit.

Statistical analysis title	Primary efficacy endpoint
Comparison groups	DKP.TRIS/TRAM.HCl v TRAM.HCl/ Paracetamol
Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Secondary: Percentage of patients achieving at least 50% of max TOTPAR at 6 hours post dose

End point title	Percentage of patients achieving at least 50% of max TOTPAR at 6 hours post dose

End point description:

Responders were defined as those patients having achieved at least at least 50% max TOTPAR at each pre-specified time point.

End point type	Secondary

End point timeframe:

at 6 hours after the treatment intake

End point values	DKP.TRIS/TRAM.HCl	TRAM.HCl/ Paracetamol	Placebo	ITT population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	260	262	131	653
Units: patients	157	101	5	263

Statistical analyses

Statistical analysis title	Secondary efficacy endpoint
Comparison groups	DKP.TRIS/TRAM.HCl v TRAM.HCl/ Paracetamol v Placebo
Number of subjects included in analysis	653
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Secondary: Sum of Pain Intensity Differences over 6 hours post dose (SPID 6)

End point title	Sum of Pain Intensity Differences over 6 hours post dose (SPID 6)

End point description:

Sum of Pain Intensity Differences, calculated as the weighted sum of the PID values, over 6 hours after treatment intake (SPID6)

End point type	Secondary

End point timeframe:

over 6 hours after the treatment intake

End point values	DKP.TRIS/TRAM.HCl	TRAM.HCl/ Paracetamol	Placebo	ITT population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	260	262	131	653
Units: points on a scale				
arithmetic mean (standard deviation)	18.4 (± 11.09)	11.7 (± 11.58)	1.6 (± 6.72)	12.3 (± 12.22)

Statistical analyses

Statistical analysis title	Secondary efficacy endpoint
Comparison groups	DKP.TRIS/TRAM.HCl v TRAM.HCl/ Paracetamol v Placebo
Number of subjects included in analysis	653
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE were collected throughout the whole duration of the study. At each visit patients were asked a standard question to elicit medically related changes in their well-being. Abnormal laboratory findings judged as clinically significant were considered AE.

Adverse event reporting additional description:

All the AEs were recorded in source documents and eCRF.
The causality of AEs was assessed based on following algorithm:
1.certanly
2.probably
3.possibly
4.unlikely
5.not related
6.unassessable
AE ranked 1,2,3,6 were considered ADR

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	DKP.TRIS/TRAM.HCl

Reporting group description:

Dexketoprofen trometamol/Tramadol hydrochloride 25mg /75mg fixed dose combination oral tablet single dose

Reporting group title	TRAM.HCl/ Paracetamol

Reporting group description:

Tramadol / Paracetamol 75mg/650mg as 2 x [37.5 mg/325 mg] fixed dose combination oral tablets single dose.

Reporting group title	Placebo

Reporting group description:

- Placebo matching DKP.TRIS/TRAM.HCl 25mg/75 mg film-coated oral tablet
- Placebo matching TRAM.HCl/Paracetamol 75mg/650mg as 2 x [37.5 mg/325 mg] film-coated oral tablets.

Serious adverse events	DKP.TRIS/TRAM.HCl	TRAM.HCl/ Paracetamol	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 260 (0.38%)	0 / 262 (0.00%)	0 / 131 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Syncope	Additional description: The SAE was upgraded to "serious" by the Sponsor as per "Important Medical Event" seriousness criteria, the event, consisting in syncope of mild intensity, resolved spontaneously. The event was assessed as "not related" to the study medication.		
subjects affected / exposed	1 / 260 (0.38%)	0 / 262 (0.00%)	0 / 131 (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: 2 %

Non-serious adverse events	DKP.TRIS/TRAM.HCl	TRAM.HCl/ Paracetamol	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 260 (18.08%)	54 / 262 (20.61%)	20 / 131 (15.27%)
Vascular disorders			
Haematoma			
subjects affected / exposed	2 / 260 (0.77%)	0 / 262 (0.00%)	3 / 131 (2.29%)
occurrences (all)	2	0	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 260 (2.69%)	13 / 262 (4.96%)	0 / 131 (0.00%)
occurrences (all)	7	13	0
Somnolence			
subjects affected / exposed	8 / 260 (3.08%)	5 / 262 (1.91%)	1 / 131 (0.76%)
occurrences (all)	8	5	1
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	3 / 260 (1.15%)	8 / 262 (3.05%)	4 / 131 (3.05%)
occurrences (all)	3	8	4
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	10 / 260 (3.85%)	12 / 262 (4.58%)	0 / 131 (0.00%)
occurrences (all)	10	12	0
Vomiting			
subjects affected / exposed	11 / 260 (4.23%)	14 / 262 (5.34%)	0 / 131 (0.00%)
occurrences (all)	11	14	0
Infections and infestations			
Postoperative wound infection			
subjects affected / exposed	8 / 260 (3.08%)	2 / 262 (0.76%)	2 / 131 (1.53%)
occurrences (all)	8	2	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported