Clinical trial results:
A randomized, double-blind, placebo-controlled, parallel arm group study to evaluate the analgesic efficacy and safety of dexketoprofen trometamol and tramadol hydrochloride oral fixed dose combination on moderate to severe acute pain in patients with acute low back pain – DANTE study

Summary

EudraCT number	2019-003656-37
Trial protocol	EE PL ES HU LV HR
Global end of trial date	04 May 2022

Results information

Result version number	v1 (current)
This version publication date	04 June 2023
First version publication date	04 June 2023

Trial information

Trial identification

Sponsor protocol code	MEIN/18/DEX-LBP/001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05170841
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Menarini International Operation Luxembourg SA
Sponsor organisation address	1, Avenue de la Gare, Luxembourg, Luxembourg, L-1611
Public contact	Clinical Operation Director, Menarini International Operations Luxembourg SA, +39 055 568091, pfabrizzi@menarini.it
Scientific contact	Clinical Operation Director, Menarini International Operations Luxembourg SA, +39 055 568091, pfabrizzi@menarini.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	20 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 May 2022
Global end of trial reached?	Yes
Global end of trial date	04 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the analgesic efficacy of Desketoprofen/Tramadol fixed combination versus placebo in moderate to severe acute low back pain after the first dose (first 8 hours).

Protection of trial subjects:

The study was conducted in accordance with the study protocol, the recommendations on biomedical research on human patients of the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, European Union (EU)-Directives and Regulations, and national requirements of the participating countries.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 September 2020
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: 351
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Croatia: 92
Country: Number of subjects enrolled	Estonia: 19
Country: Number of subjects enrolled	Hungary: 65
Country: Number of subjects enrolled	Latvia: 10
Worldwide total number of subjects	538
EEA total number of subjects	538

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)	534
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study started on 17 September and terminated on 4 May 2022
Number of screened patients: 544
Number of randomized patients: 538
Number of screen failures: 6 patients
Number of drop out patients: 14
524 patients completed the study

Pre-assignment

Screening details:

Male or female patients aged 18 years to 65 years with acute low back pain of moderate to severe intensity, whose onset of the current acute low back pain episode was within 48 hours prior to Screening. Patients with or without radiculopathy were included, excluding those with neurological signs, according to the Quebec Task Force classification.

Period 1

Period 1 title	Single dose Phase - Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Double-dummy design was applied to ensure a double-blind condition of DKP.TRIS 25 mg / TRAM.HCl 75 mg versus TRAM.HCl 100 mg versus the respective placebos. The placebo tablets were provided as film-coated tablets with appearance and weight matching relative DKP.TRIS 25 mg / TRAM.HCl 75 mg. The active comparator, TRAM.HCl 100 mg, was provided as 2 capsules of Tramadol 50 mg and, for blinding purpose, 2 capsules of placebo were provided with appearance and weight matching relative Tramadol 50 mg.

Arms

Are arms mutually exclusive?	Yes
Arm title	Desketoprofen 25mg/Tramadol 75mg

Arm description:

In the single-dose phase (Period 1), the patients received a single-dose treatment, consisted of 1-film-coated tablet and 2 capsules which were orally administered together at the same time on Day 1 according to the Investigator’s instructions.

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

Dosage and administration details:

1-film-coated tablet orally administered together on Day 1 according to the Investigator’s instructions

Arm title	Tramadol 100mg

Arm description:

In the single-dose phase (Period 1), the patients received a single-dose treatment, consisted of 1-film-coated tablet and 2 capsules which were orally administered together at the same time on Day 1 according to the Investigator’s instructions

Arm type	Active comparator

Investigational medicinal product name	Tramadol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 capsules orally administered together on Day 1 according to the Investigator’s instructions

Arm title	Placebo Desketoprofen/Tramadol

Arm description:

In the single-dose phase (Period 1), the patients received a single-dose treatment, consisted of 1-film-coated tablet and 2 capsules which were orally administered together at the same time on Day 1 according to the Investigator’s instructions

Arm type	Placebo
Investigational medicinal product name	Placebo Desketoprofen/Tramadol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1-film-coated tablet orally administered together on Day 1 according to the Investigator’s instructions

Arm title	Placebo Tramadol

Arm description:

In the single-dose phase (Period 1), the patients received a single-dose treatment, consisted of 1-film-coated tablet and 2 capsules which were orally administered together at the same time on Day 1 according to the Investigator’s instructions

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

Dosage and administration details:

2 capsules orally administered together on Day 1 according to the Investigator’s instructions

Number of subjects in period 1	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100mg	Placebo Desketoprofen/Tramadol
Started	211	207	59
Completed	209	202	58
Not completed	2	5	1
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	2	4	1

Number of subjects in period 1	Placebo Tramadol
Started	61
Completed	55
Not completed	6
Consent withdrawn by subject	-

Adverse event, non-fatal	6

Period 2

Period 2 title	Multiple Dose Phase - Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Desketoprofen 25mg/Tramadol 75mg

Arm description:

The multiple-dose phase (Period 2) began 8 h after the first dose. The patients assigned to Desketoprofen 25mg/Tramadol 75mg fixed combination or Tramadol 100mg during the single-dose phase continued to receive the same treatment during the multiple-dose phase; however, the patients assigned to receive placebo during the single-dose phase either received Desketoprofen 25mg/Tramadol 75mg fixed combination or Tramadol 100mg every 8 h during the multiple-dose phase. A total of 12 doses of study treatment were administered, with the last study medication intake administered within Day 5

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

Dosage and administration details:

1-film-coated tablet orally administered together according to the Investigator’s instructions

Arm title	Tramadol 100 mg

Arm description:

The multiple-dose phase (Period 2) began 8 h after the first dose. The patients assigned to Desketoprofen 25mg/Tramadol 75mg fixed combination or Tramadol 100mg during the single-dose phase continued to receive the same treatment during the multiple-dose phase; however, the patients assigned to receive placebo during the single-dose phase either received Desketoprofen 25mg/Tramadol 75mg fixed combination or Tramadol 100mg every 8 h during the multiple-dose phase. A total of 12 doses of study treatment were administered, with the last study medication intake administered within Day 5

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

Dosage and administration details:

2 capsules orally administered together according to the Investigator’s instructions

Arm title	Desketoprofen 25mg/Tramadol 75mg

Arm description:

The multiple-dose phase (Period 2) began 8 h after the first dose. The patients assigned to Desketoprofen 25mg/Tramadol 75mg fixed combination or Tramadol 100mg during the single-dose phase continued to receive the same treatment during the multiple-dose phase; however, the patients assigned to receive placebo during the single-dose phase either received Desketoprofen 25mg/Tramadol 75mg fixed combination or Tramadol 100mg every 8 h during the multiple-dose phase. A total of 12 doses of study treatment were administered, with the last study medication intake administered within Day 5

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

Dosage and administration details:

1-film-coated tablet orally administered together according to the Investigator’s instructions

Arm title	Tramadol 100 mg

Arm description:

The multiple-dose phase (Period 2) began 8 h after the first dose. The patients assigned to Desketoprofen 25mg/Tramadol 75mg fixed combination or Tramadol 100mg during the single-dose phase continued to receive the same treatment during the multiple-dose phase; however, the patients assigned to receive placebo during the single-dose phase either received Desketoprofen 25mg/Tramadol 75mg fixed combination or Tramadol 100mg every 8 h during the multiple-dose phase. A total of 12 doses of study treatment were administered, with the last study medication intake administered within Day 5

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

Dosage and administration details:

2 capsules orally administered together according to the Investigator’s instructions

Number of subjects in period 2	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg	Desketoprofen 25mg/Tramadol 75mg
Started	209	202	58
Completed	209	202	58

Number of subjects in period 2	Tramadol 100 mg
Started	55
Completed	55

Baseline characteristics

Reporting groups	
Reporting group title	Desketoprofen 25mg/Tramadol 75mg
Reporting group description:	
In the single-dose phase (Period 1), the patients received a single-dose treatment, consisted of 1-film-coated tablet and 2 capsules which were orally administered together at the same time on Day 1 according to the Investigator's instructions.	
Reporting group title	Tramadol 100mg
Reporting group description:	
In the single-dose phase (Period 1), the patients received a single-dose treatment, consisted of 1-film-coated tablet and 2 capsules which were orally administered together at the same time on Day 1 according to the Investigator's instructions	
Reporting group title	Placebo Desketoprofen/Tramadol
Reporting group description:	
In the single-dose phase (Period 1), the patients received a single-dose treatment, consisted of 1-film-coated tablet and 2 capsules which were orally administered together at the same time on Day 1 according to the Investigator's instructions	
Reporting group title	Placebo Tramadol
Reporting group description:	
In the single-dose phase (Period 1), the patients received a single-dose treatment, consisted of 1-film-coated tablet and 2 capsules which were orally administered together at the same time on Day 1 according to the Investigator's instructions	

Reporting group values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100mg	Placebo Desketoprofen/Tramadol
Number of subjects	211	207	59
Age categorical Units: Subjects			
Adults (18-64 years)	210	205	58
From 65-84 years	1	2	1
Gender categorical Units: Subjects			
Female	98	101	28
Male	113	106	31

Reporting group values	Placebo Tramadol	Total	
Number of subjects	61	538	
Age categorical Units: Subjects			
Adults (18-64 years)	61	534	
From 65-84 years	0	4	
Gender categorical Units: Subjects			
Female	28	255	
Male	33	283	

Subject analysis sets	
Subject analysis set title	Modified IIT Population (mIIT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified intent-to-treat (mITT) population included the first cohort of 510 patients randomized to the 4 treatment arms (204 patients in the DesKetoprofen 25mg/Tramadol 75mg arms + 204 patients in the Tramadol 100mg arms + 51 patients in the Placebo DesKetoprofen/Tramadol arm and 51 patients in the Placebo Tramadol arm) in a 4:4:1:1 ratio.

Subject analysis set title	Per Protocol (PP) Population
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol (PP) population included all patients in the ITT who had not experienced major protocol violations that could affect the primary efficacy analysis. Protocol violations which had a major distorting influence on the primary endpoints resulted in patients being excluded from the PP population (465 patients totally). The PDs identified during the clinical conduct of the study, as authorised in the final PD log, were taken into consideration in the final assignment of patients to the analysis sets. Patients were assigned to the treatment received, for each category in case the treatment received differs from that randomized.

Reporting group values	Modified IIT Population (mIIT)	Per Protocol (PP) Population	
Number of subjects	510	465	
Age categorical Units: Subjects			
Adults (18-64 years)	506	464	
From 65-84 years	4	1	
Gender categorical Units: Subjects			
Female	236	220	
Male	274	245	

End points

End points reporting groups

Reporting group title	Desketoprofen 25mg/Tramadol 75mg

Reporting group description:

In the single-dose phase (Period 1), the patients received a single-dose treatment, consisted of 1-film-coated tablet and 2 capsules which were orally administered together at the same time on Day 1 according to the Investigator’s instructions.

Reporting group title	Tramadol 100mg

Reporting group description:

In the single-dose phase (Period 1), the patients received a single-dose treatment, consisted of 1-film-coated tablet and 2 capsules which were orally administered together at the same time on Day 1 according to the Investigator’s instructions

Reporting group title	Placebo Desketoprofen/Tramadol

Reporting group description:

In the single-dose phase (Period 1), the patients received a single-dose treatment, consisted of 1-film-coated tablet and 2 capsules which were orally administered together at the same time on Day 1 according to the Investigator’s instructions

Reporting group title	Placebo Tramadol

Reporting group description:

In the single-dose phase (Period 1), the patients received a single-dose treatment, consisted of 1-film-coated tablet and 2 capsules which were orally administered together at the same time on Day 1 according to the Investigator’s instructions

Reporting group title	Desketoprofen 25mg/Tramadol 75mg

Reporting group description:

The multiple-dose phase (Period 2) began 8 h after the first dose. The patients assigned to Desketoprofen 25mg/Tramadol 75mg fixed combination or Tramadol 100mg during the single-dose phase continued to receive the same treatment during the multiple-dose phase; however, the patients assigned to receive placebo during the single-dose phase either received Desketoprofen 25mg/Tramadol 75mg fixed combination or Tramadol 100mg every 8 h during the multiple-dose phase. A total of 12 doses of study treatment were administered, with the last study medication intake administered within Day 5

Reporting group title	Tramadol 100 mg

Reporting group description:

The multiple-dose phase (Period 2) began 8 h after the first dose. The patients assigned to Desketoprofen 25mg/Tramadol 75mg fixed combination or Tramadol 100mg during the single-dose phase continued to receive the same treatment during the multiple-dose phase; however, the patients assigned to receive placebo during the single-dose phase either received Desketoprofen 25mg/Tramadol 75mg fixed combination or Tramadol 100mg every 8 h during the multiple-dose phase. A total of 12 doses of study treatment were administered, with the last study medication intake administered within Day 5

Reporting group title	Desketoprofen 25mg/Tramadol 75mg

Reporting group description:

The multiple-dose phase (Period 2) began 8 h after the first dose. The patients assigned to Desketoprofen 25mg/Tramadol 75mg fixed combination or Tramadol 100mg during the single-dose phase continued to receive the same treatment during the multiple-dose phase; however, the patients assigned to receive placebo during the single-dose phase either received Desketoprofen 25mg/Tramadol 75mg fixed combination or Tramadol 100mg every 8 h during the multiple-dose phase. A total of 12 doses of study treatment were administered, with the last study medication intake administered within Day 5

Reporting group title	Tramadol 100 mg

Reporting group description:

The multiple-dose phase (Period 2) began 8 h after the first dose. The patients assigned to Desketoprofen 25mg/Tramadol 75mg fixed combination or Tramadol 100mg during the single-dose phase continued to receive the same treatment during the multiple-dose phase; however, the patients assigned to receive placebo during the single-dose phase either received Desketoprofen 25mg/Tramadol 75mg fixed combination or Tramadol 100mg every 8 h during the multiple-dose phase. A total of 12 doses of study treatment were administered, with the last study medication intake administered within Day 5

Subject analysis set title	Modified IIT Population (mIIT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The modified intent-to-treat (mITT) population included the first cohort of 510 patients randomized to the 4 treatment arms (204 patients in the DesKetoprofen 25mg/Tramadol 75mg arms + 204 patients in the Tramadol 100mg arms + 51 patients in the Placebo DesKetoprofen/Tramadol arm and 51 patients in the Placebo Tramadol arm) in a 4:4:1:1 ratio.

Subject analysis set title	Per Protocol (PP) Population
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol (PP) population included all patients in the ITT who had not experienced major protocol violations that could affect the primary efficacy analysis. Protocol violations which had a major distorting influence on the primary endpoints resulted in patients being excluded from the PP population (465 patients totally). The PDs identified during the clinical conduct of the study, as authorised in the final PD log, were taken into consideration in the final assignment of patients to the analysis sets. Patients were assigned to the treatment received, for each category in case the treatment received differs from that randomized.

Primary: Time to first achieve an NRS-PI score < 4 or a pain intensity reduction of ≥ 30% from drug intake till 8 h after the first dose (t8h)

End point title	Time to first achieve an NRS-PI score < 4 or a pain intensity reduction of ≥ 30% from drug intake till 8 h after the first dose (t8h)[1]

End point description:

To evaluate the analgesic efficacy of Desketoprofen 25mg/Tramadol 75mg fixed combination versus placebo in moderate to severe acute Low Back Pain during the Single Dose Phase - Period 1 (first 8 h after first intake).

End point type	Primary

End point timeframe:

From T=0 to T=8h

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms involved in the analysis are not all the ones in the baseline period but alternatively: Desketo/Tramadol (experimental) vs Tramadol or Desketo/Tramadol vs Placebo both in the Single dose Phase (Period 1) or in the Multiple Dose Phase (Period 2) depending on the endpoint calculated.

End point values	Desketoprofen 25mg/Tramadol 75mg	Placebo Desketoprofen/Tramadol	Placebo Tramadol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204	51	51	
Units: Minutes				
arithmetic mean (full range (min-max))	105 (15 to 480)	120 (15 to 360)	120 (15 to 360)	

Statistical analyses

Statistical analysis title	Desk/Tram vs placebo in mIIT Population

Statistical analysis description:

Single Dose Phase (Period 1) analysis. Time to first achieve an NRS-PI score < 4 or a pain intensity reduction of ≥ 30% from drug intake of Desketoprofen 25mg/Tramadol 75mg vs Placebo Desketoprofen/Tramadol and Placebo Tramadol 8 h after the first dose intake. Analysis conducted in the mIIT Population.

Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Placebo Desketoprofen/Tramadol v Placebo Tramadol

Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.566
Method	t-test, 2-sided

Secondary: Total pain relief vs Tramadol at 4h

End point title	Total pain relief vs Tramadol at 4h[2]

End point description:

Total pain relief (TOTPAR) at 4 h after the first dose. TOTPAR was calculated as the time-weighted sum of the PAR-VRS scores

End point type	Secondary

End point timeframe:

From T=0 to T=4h

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms involved in the analysis are not all the ones in the baseline period but alternatively: Desketo/Tramadol (experimental) vs Tramadol or Desketo/Tramadol vs Placebo both in the Single dose Phase (Period 1) or in the Multiple Dose Phase (Period 2) depending on the endpoint calculated.

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	202		
Units: Par Vrs scores				
arithmetic mean (standard deviation)	4.6 (± 3.6)	3.8 (± 2.84)		

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Tramadol in mIIT population

Statistical analysis description:

Single Dose Phase (Period 1) analysis

Comparison groups	Tramadol 100mg v Desketoprofen 25mg/Tramadol 75mg
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	t-test, 2-sided

Secondary: Tot par vs Tramadolo at 6h

End point title	Tot par vs Tramadolo at 6h[3]

End point description:

Total pain relief (TOTPAR) at 6 h after the first dose. TOTPAR was calculated as the time-weighted sum of the PAR-VRS scores

End point type	Secondary

End point timeframe:

From T=0 to T=6h

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms involved in the analysis are not all the ones in the baseline period but alternatively: Desketo/Tramadol (experimental) vs Tramadol or Desketo/Tramadol vs Placebo both in the Single dose Phase (Period 1) or in the Multiple Dose Phase (Period 2) depending on the endpoint calculated.

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	203		
Units: PAR-VRS scores				
arithmetic mean (standard deviation)	7.4 (± 5.52)	6.0 (± 4.41)		

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Tramadol in mIIT population

Statistical analysis description:

Single Dose Phase (Period 1) analysis

Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Tramadol 100mg
Number of subjects included in analysis	407
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	t-test, 2-sided

Secondary: Tot par vs Tramadolo 8h

End point title	Tot par vs Tramadolo 8h[4]

End point description:

Total pain relief (TOTPAR) at 8 h after the first dose. TOTPAR was calculated as the time-weighted sum of the PAR-VRS scores

End point type	Secondary

End point timeframe:

From T=0 to T=8h

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms involved in the analysis are not all the ones in the baseline period but alternatively: Desketo/Tramadol (experimental) vs Tramadol or Desketo/Tramadol vs Placebo both in the Single dose Phase (Period 1) or in the Multiple Dose Phase (Period 2) depending on the endpoint calculated.

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	204		
Units: Par-Vrs Scores				
arithmetic mean (standard deviation)	10.1 (± 7.18)	8.5 (± 5.92)		

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Tramadol in mIIT population
Statistical analysis description:	
Single Dose Phase (Period 1) analysis.	
Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Tramadol 100mg
Number of subjects included in analysis	408
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	t-test, 2-sided

Secondary: Tot Par vs Placebo at 6h

End point title	Tot Par vs Placebo at 6h[5]
End point description:	
Total pain relief (TOTPAR) at 6 h after the first dose. TOTPAR was calculated as the time-weighted sum of the PAR-VRS scores	
End point type	Secondary
End point timeframe:	
From T=0 to T=6h	

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms involved in the analysis are not all the ones in the baseline period but alternatively: Desketo/Tramadol (experimental) vs Tramadol or Desketo/Tramadol vs Placebo both in the Single dose Phase (Period 1) or in the Multiple Dose Phase (Period 2) depending on the endpoint calculated.

End point values	Desketoprofen 25mg/Tramadol 75mg	Placebo Desketoprofen/ Tramadol	Placebo Tramadol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204	51	51	
Units: Par VRS scores				
arithmetic mean (standard deviation)	7.4 (± 5.52)	6.1 (± 4.37)	6.1 (± 4.37)	

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Placebo in mIIT Population

Statistical analysis description: Single Dose Phase (Period 1) analysis.	
Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Placebo Desketoprofen/Tramadol v Placebo Tramadol
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031
Method	t-test, 2-sided

Secondary: Tot Par vs Placebo at 8h

End point title	Tot Par vs Placebo at 8h[6]
End point description: Total pain relief (TOTPAR) at 8h after the first dose. TOTPAR was calculated as the time-weighted sum of the PAR-VRS scores	
End point type	Secondary
End point timeframe: From T=0 to T=8h	

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms involved in the analysis are not all the ones in the baseline period but alternatively: Desketo/Tramadol (experimental) vs Tramadol or Desketo/Tramadol vs Placebo both in the Single dose Phase (Period 1) or in the Multiple Dose Phase (Period 2) depending on the endpoint calculated.

End point values	Desketoprofen 25mg/Tramadol 75mg	Placebo Desketoprofen/Tramadol	Placebo Tramadol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204	51	51	
Units: Par Vrs score				
arithmetic mean (standard deviation)	10.1 (± 7.18)	8.4 (± 5.81)	8.4 (± 5.81)	

Statistical analyses

Statistical analysis title	Desketo/Tramadolo vs Placebo in mIIT Population
Statistical analysis description: Single Dose Phase (Period 1) analysis	
Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Placebo Desketoprofen/Tramadol v Placebo Tramadol
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027
Method	t-test, 2-sided

Secondary: % Patients achieving at least 50% Max TotPar vs Tramadolo at 4h

End point title	% Patients achieving at least 50% Max TotPar vs Tramadolo at 4h[7]

End point description:

Percentage of patients achieving at least 50% of maximum Total Pain Relief (TOTPAR) at 4 h after the first dose in Desketoprofen 25mg/Tramadol 75mg arm as compared with Tramadol 100mg arm (Single Dose Phase - Period 1)

End point type	Secondary

End point timeframe:

From T=0 to T=4h

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms involved in the analysis are not all the ones in the baseline period but alternatively: Desketo/Tramadol (experimental) vs Tramadol or Desketo/Tramadol vs Placebo both in the Single dose Phase (Period 1) or in the Multiple Dose Phase (Period 2) depending on the endpoint calculated.

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	204		
Units: percentage				
number (not applicable)	20.6	8.8		

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Tramadol in mIIT Population

Statistical analysis description:

Single Dose Phase (Period 1) analysis

Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Tramadol 100mg
Number of subjects included in analysis	408
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 2-sided

Secondary: % patients achieving at least 50% Max Totpar vs Tramadolo at 6h

End point title	% patients achieving at least 50% Max Totpar vs Tramadolo at 6h[8]

End point description:

Percentage of patients achieving at least 50% of maximum Total Pain Relief (TOTPAR) at 6 h after the first dose in Desketoprofen 25mg/Tramadol 75mg arm as compared with Tramadol 100mg arm (Single Dose Phase - Period 1)

End point type	Secondary

End point timeframe:

From T=0 to T=6h

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms involved in the analysis are not all the ones in the baseline period but alternatively: Desketo/Tramadol (experimental) vs Tramadol or Desketo/Tramadol vs Placebo both in the Single dose

Phase (Period 1) or in the Multiple Dose Phase (Period 2) depending on the endpoint calculated.

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	204		
Units: Percentage				
number (not applicable)	22.5	9.8		

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Tramadol in mIIT Population
Statistical analysis description: Single Dose Phase (Period 1) analysis.	
Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Tramadol 100mg
Number of subjects included in analysis	408
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 2-sided

Secondary: % Patinets achieving at least 50% of Max TotPar vs Tramadolo at 8h

End point title	% Patinets achieving at least 50% of Max TotPar vs Tramadolo at 8h[9]

End point description:

Percentage of patients achieving at least 50% of maximum Total Pain Relief (TOTPAR) at 8 h after the first dose in Desketoprofen 25mg/Tramadol 75mg arm as compared with Tramadol 100mg arm (Single Dose Phase - Period 1)

End point type	Secondary

End point timeframe:

From T=0 to T=8h

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms involved in the analysis are not all the ones in the baseline period but alternatively: Desketo/Tramadol (experimental) vs Tramadol or Desketo/Tramadol vs Placebo both in the Single dose Phase (Period 1) or in the Multiple Dose Phase (Period 2) depending on the endpoint calculated.

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	204		
Units: percentage				
number (not applicable)	23.5	11.3		

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Tramadol in mIIT Population
Statistical analysis description: Single Dose Phase (Period 1) analysis	
Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Tramadol 100mg
Number of subjects included in analysis	408
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	t-test, 2-sided

Secondary: % Patients achieving at least 50% of Max TOTPAR vs Placebo at 4h

End point title	% Patients achieving at least 50% of Max TOTPAR vs Placebo at 4h[10]
End point description: Percentage of patients achieving at least 50% of maximum Total Pain Relief (TOTPAR) at 4 h after the first dose in Desketoprofen 25mg/Tramadol 75mg arm as compared with Placebo arms (Single Dose Phase - Period 1)	
End point type	Secondary
End point timeframe: From T=0 to T=4h	

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms involved in the analysis are not all the ones in the baseline period but alternatively: Desketo/Tramadol (experimental) vs Tramadol or Desketo/Tramadol vs Placebo both in the Single dose Phase (Period 1) or in the Multiple Dose Phase (Period 2) depending on the endpoint calculated.

End point values	Desketoprofen 25mg/Tramadol 75mg	Placebo Desketoprofen/ Tramadol	Placebo Tramadol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204	51	51	
Units: percentage				
number (not applicable)	20.6	8.8	8.8	

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Placebo in mIIT Population
Statistical analysis description: Single Dose Phase (Period 1) analysis	

Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Placebo Desketoprofen/Tramadol v Placebo Tramadol
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	t-test, 2-sided

Secondary: % Patients achieving at least 50% of Max TOTPAR vs Placebo at 6h

End point title	% Patients achieving at least 50% of Max TOTPAR vs Placebo at 6h[11]

End point description:

Percentage of patients achieving at least 50% of maximum Total Pain Relief (TOTPAR) at 6 h after the first dose in Desketoprofen 25mg/Tramadol 75mg arm as compared with Placebo arms (Single Dose Phase - Period 1)

End point type	Secondary

End point timeframe:

From T=0 to T=6h

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms involved in the analysis are not all the ones in the baseline period but alternatively: Desketo/Tramadol (experimental) vs Tramadol or Desketo/Tramadol vs Placebo both in the Single dose Phase (Period 1) or in the Multiple Dose Phase (Period 2) depending on the endpoint calculated.

End point values	Desketoprofen 25mg/Tramadol 75mg	Placebo Desketoprofen/ Tramadol	Placebo Tramadol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204	51	51	
Units: percentage				
number (not applicable)	22.5	8.8	8.8	

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Placebo in mIIT Population

Statistical analysis description:

Single Dose Phase (Period 1) analysis

Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Placebo Desketoprofen/Tramadol v Placebo Tramadol
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	t-test, 2-sided

Secondary: % Patients achieving at least 50% of Max TOTPAR vs Placebo at 8h

End point title	% Patients achieving at least 50% of Max TOTPAR vs Placebo at 8h[12]

End point description:

Percentage of patients achieving at least 50% of maximum Total Pain Relief (TOTPAR) at 8 h after the first dose in Desketoprofen 25mg/Tramadol 75mg arm as compared with Placebo arms (Single Dose Phase - Period 1)

End point type	Secondary

End point timeframe:

From T=0 to T=8h

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms involved in the analysis are not all the ones in the baseline period but alternatively: Desketo/Tramadol (experimental) vs Tramadol or Desketo/Tramadol vs Placebo both in the Single dose Phase (Period 1) or in the Multiple Dose Phase (Period 2) depending on the endpoint calculated.

End point values	Desketoprofen 25mg/Tramadol 75mg	Placebo Desketoprofen/Tramadol	Placebo Tramadol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204	51	51	
Units: Percentage				
number (not applicable)	23.5	11.8	11.8	

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Placebo in mIIT Population

Statistical analysis description:

Single Dose Phase (Period 1) analysis

Comparison groups	Placebo Desketoprofen/Tramadol v Desketoprofen 25mg/Tramadol 75mg v Placebo Tramadol
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	t-test, 2-sided

Secondary: % Max Totpar vs Tramadol at 4h

End point title	% Max Totpar vs Tramadol at 4h[13]

End point description:

The max TOTPAR was calculated as the theoretical maximum time-weighted sum of the PAR values for each patient. The maximum possible TOTPAR was the value of TOTPAR that would have been obtained if the patient had a complete pain relief for that observation period (Single Dose Phase - Period 1)

End point type	Secondary

End point timeframe:

From T=0 to T=4h

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms involved in the analysis are not all the ones in the baseline period but alternatively: Desketo/Tramadol (experimental) vs Tramadol or Desketo/Tramadol vs Placebo both in the Single dose Phase (Period 1) or in the Multiple Dose Phase (Period 2) depending on the endpoint calculated.

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	203		
Units: Percentage				
arithmetic mean (standard deviation)	29.1 (± 22.57)	24.1 (± 17.92)		

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Tramadol in mTT Population
Statistical analysis description: Single Dose Phase (Period 1) analysis	
Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Tramadol 100mg
Number of subjects included in analysis	407
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	t-test, 2-sided

Secondary: % Max Totpar vs Tramadol at 6h

End point title	% Max Totpar vs Tramadol at 6h[14]
End point description: The max TOTPAR was calculated as the theoretical maximum time-weighted sum of the PAR values for each patient. The maximum possible TOTPAR was the value of TOTPAR that would have been obtained if the patient had a complete pain relief for that observation period (Single Dose Phase - Period 1)	
End point type	Secondary
End point timeframe: From T=0 to T=6h	

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms involved in the analysis are not all the ones in the baseline period but alternatively: Desketo/Tramadol (experimental) vs Tramadol or Desketo/Tramadol vs Placebo both in the Single dose Phase (Period 1) or in the Multiple Dose Phase (Period 2) depending on the endpoint calculated.

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	203		
Units: Percentage				
arithmetic mean (standard deviation)	30.9 (± 23.04)	25.5 (± 18.56)		

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Tramadol in mIIT Population
Statistical analysis description: Single Dose Phase (Period 1) analysis	
Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Tramadol 100mg
Number of subjects included in analysis	407
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	t-test, 2-sided

Secondary: % Max Totpar vs Tramadol at 8h

End point title	% Max Totpar vs Tramadol at 8h[15]

End point description:

The max TOTPAR was calculated as the theoretical maximum time-weighted sum of the PAR values for each patient. The maximum possible TOTPAR was the value of TOTPAR that would have been obtained if the patient had a complete pain relief for that observation period (Single Dose Phase - Period 1)

End point type	Secondary

End point timeframe:

From T=0 to T=8h

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms involved in the analysis are not all the ones in the baseline period but alternatively: Desketo/Tramadol (experimental) vs Tramadol or Desketo/Tramadol vs Placebo both in the Single dose Phase (Period 1) or in the Multiple Dose Phase (Period 2) depending on the endpoint calculated.

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204	204		
Units: Percentage				
arithmetic mean (standard deviation)	32.1 (± 22.75)	27.1 (± 18.59)		

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Tramadol in mIIT Population
Statistical analysis description: Single Dose Phase (Period 1) analysis	
Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Tramadol 100mg
Number of subjects included in analysis	408
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	t-test, 2-sided

Secondary: % Max Totpar vs Placebo at 6h

End point title	% Max Totpar vs Placebo at 6h[16]
End point description: The max TOTPAR was calculated as the theoretical maximum time-weighted sum of the PAR values for each patient. The maximum possible TOTPAR was the value of TOTPAR that would have been obtained if the patient had a complete pain relief for that observation period (Single Dose Phase - Period 1)	
End point type	Secondary
End point timeframe: From t=0 to T=6h	

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms involved in the analysis are not all the ones in the baseline period but alternatively: Desketo/Tramadol (experimental) vs Tramadol or Desketo/Tramadol vs Placebo both in the Single dose Phase (Period 1) or in the Multiple Dose Phase (Period 2) depending on the endpoint calculated.

End point values	Desketoprofen 25mg/Tramadol 75mg	Placebo Desketoprofen/ Tramadol	Placebo Tramadol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204	51	50	
Units: Percentage				
arithmetic mean (standard deviation)	30.9 (± 23.4)	25.5 (± 18.12)	25.5 (± 18.12)	

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Placebo in mIIT Population
Statistical analysis description: Single Dose Phase (Period 1) analysis	
Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Placebo Desketoprofen/Tramadol v Placebo Tramadol
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	t-test, 2-sided

Secondary: % Max Totpar vs Placebo at 8h

End point title	% Max Totpar vs Placebo at 8h[17]

End point description:

The max TOTPAR was calculated as the theoretical maximum time-weighted sum of the PAR values for each patient. The maximum possible TOTPAR was the value of TOTPAR that would have been obtained if the patient had a complete pain relief for that observation period (Single Dose Phase - Period 1)

End point type	Secondary

End point timeframe:

From T=0 to T=8h

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms involved in the analysis are not all the ones in the baseline period but alternatively: Desketo/Tramadol (experimental) vs Tramadol or Desketo/Tramadol vs Placebo both in the Single dose Phase (Period 1) or in the Multiple Dose Phase (Period 2) depending on the endpoint calculated.

End point values	Desketoprofen 25mg/Tramadol 75mg	Placebo Desketoprofen/Tramadol	Placebo Tramadol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204	51	51	
Units: Percentage				
arithmetic mean (standard deviation)	32.1 (± 22.75)	26.4 (± 18.03)	26.4 (± 18.03)	

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Placebo in mIIT Population

Statistical analysis description:

Single Dose Phase (Period 1) analysis

Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Placebo Desketoprofen/Tramadol v Placebo Tramadol
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	t-test, 2-sided

Secondary: Multiple Dose Phase - Totpar vs Tramadolo at 24h

End point title	Multiple Dose Phase - Totpar vs Tramadolo at 24h

End point description:

Total pain relief (TOTPAR) at 24 h after the first dose. TOTPAR was calculated as the time-weighted sum of the PAR-VRS scores

End point type	Secondary

End point timeframe:

From T=0 to T=24h

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	201	202	43	48
Units: Par Vrs scores				
arithmetic mean (standard deviation)	44.6 (± 20.20)	40.9 (± 19.85)	44.6 (± 20.20)	40.9 (± 19.85)

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Tramadol in mIIT Population
Statistical analysis description: Multiple Dose Phase (Period 2) analysis	
Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Desketoprofen 25mg/Tramadol 75mg v Tramadol 100 mg v Tramadol 100 mg
Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045
Method	t-test, 2-sided

Secondary: Multiple Dose Phase - Totpar vs Tramadolo at 48h

End point title	Multiple Dose Phase - Totpar vs Tramadolo at 48h
End point description: Total pain relief (TOTPAR) at 48 h after the first dose. TOTPAR was calculated as the time-weighted sum of the PAR-VRS scores	
End point type	Secondary
End point timeframe: From T=0 to T=48	

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	201	202	47	49
Units: Par Vrs Scores				
arithmetic mean (standard deviation)	97.8 (± 41.69)	90.0 (± 41.88)	97.8 (± 41.69)	90.0 (± 41.88)

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Tramadol in mIIT Population
Statistical analysis description: Multiple Dose Phase (Period 2) analysis	
Comparison groups	Tramadol 100 mg v Desketoprofen 25mg/Tramadol 75mg v Desketoprofen 25mg/Tramadol 75mg v Tramadol 100 mg
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042
Method	t-test, 2-sided

Secondary: Multiple Dose Phase - Totpar vs Tramadolo at 72h

End point title	Multiple Dose Phase - Totpar vs Tramadolo at 72h
End point description: Total pain relief (TOTPAR) at 72h after the first dose. TOTPAR was calculated as the time-weighted sum of the PAR-VRS scores	
End point type	Secondary
End point timeframe: From T=0 to T=72h	

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	201	202	47	49
Units: Par Vrs Scores				
arithmetic mean (standard deviation)	156.9 (± 63.83)	144.7 (± 64.14)	156.9 (± 63.83)	144.7 (± 64.14)

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Tramadol in mIIT Population
Statistical analysis description: Multiple Dose Phase (Period 2) analysis	
Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Tramadol 100 mg v Desketoprofen 25mg/Tramadol 75mg v Tramadol 100 mg
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	t-test, 2-sided

Secondary: Multiple dose Phase - % Max Totpar vs Tramadol at 24h

End point title	Multiple dose Phase - % Max Totpar vs Tramadol at 24h

End point description:

The max TOTPAR was calculated as the theoretical maximum time-weighted sum of the PAR values for each patient. The maximum possible TOTPAR was the value of TOTPAR that would have been obtained if the patient had a complete pain relief for that observation period (Multiple Dose Phase - Period 2)

End point type	Secondary

End point timeframe:

FromTt=0 to T=24

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	201	202	43	48
Units: Percentage				
arithmetic mean (standard deviation)	46.6 (± 21.07)	42.7 (± 20.66)	46.6 (± 21.07)	42.7 (± 20.66)

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Tramadol in mIIT Population

Statistical analysis description:

Multiple Dose Phase (Period 2) analysis

Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Tramadol 100 mg v Desketoprofen 25mg/Tramadol 75mg v Tramadol 100 mg
Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045
Method	t-test, 2-sided

Secondary: Multiple dose Phase - % Max Totpar vs Tramadol at 48h

End point title	Multiple dose Phase - % Max Totpar vs Tramadol at 48h

End point description:

The max TOTPAR was calculated as the theoretical maximum time-weighted sum of the PAR values for each patient. The maximum possible TOTPAR was the value of TOTPAR that would have been obtained if the patient had a complete pain relief for that observation period (Multiple Dose Phase - Period 2)

End point type	Secondary

End point timeframe:

From T=0 to T=48h

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	201	202	47	49
Units: Percentage				
arithmetic mean (standard deviation)	51.2 (± 21.69)	46.9 (± 21.79)	51.2 (± 21.69)	46.9 (± 21.79)

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Tramadol in mIIT Population
Statistical analysis description:	
Multiple Dose Phase (Period 2) analysis	
Comparison groups	Tramadol 100 mg v Desketoprofen 25mg/Tramadol 75mg v Desketoprofen 25mg/Tramadol 75mg v Tramadol 100 mg
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	t-test, 2-sided

Secondary: Multiple dose Phase - % Max Totpar vs Tramadol at 72h

End point title	Multiple dose Phase - % Max Totpar vs Tramadol at 72h
End point description:	
The max TOTPAR was calculated as the theoretical maximum time-weighted sum of the PAR values for each patient. The maximum possible TOTPAR was the value of TOTPAR that would have been obtained if the patient had a complete pain relief for that observation period (Multiple Dose Phase - Period 2)	
End point type	Secondary
End point timeframe:	
Form T=0 to T=72	

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	201	202	47	49
Units: Percentage				
arithmetic mean (standard deviation)	54.7 (± 22.15)	50.3 (± 22.24)	54.7 (± 22.15)	50.3 (± 22.24)

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Tramadol in mIIT Population
Statistical analysis description:	
Multiple Dose Phase (Period 2) analysis	

Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Tramadol 100 mg v Desketoprofen 25mg/Tramadol 75mg v Tramadol 100 mg
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027
Method	t-test, 2-sided

Secondary: Multiple dose Phase - % Max Totpar vs Tramadol at 96h

End point title	Multiple dose Phase - % Max Totpar vs Tramadol at 96h

End point description:

The max TOTPAR was calculated as the theoretical maximum time-weighted sum of the PAR values for each patient. The maximum possible TOTPAR was the value of TOTPAR that would have been obtained if the patient had a complete pain relief for that observation period (Multiple Dose Phase - Period 2)

End point type	Secondary

End point timeframe:

From t=0 to T=96

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	201	202	48	49
Units: Percentage				
arithmetic mean (standard deviation)	57.7 (± 22.7)	53.3 (± 22.82)	57.7 (± 22.7)	53.3 (± 22.82)

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Tramadol in mIIT Population

Statistical analysis description:

Multiple Dose Phase (Period 2) analysis

Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Tramadol 100 mg v Desketoprofen 25mg/Tramadol 75mg v Tramadol 100 mg
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	t-test, 2-sided

Secondary: Multiple dose Phase - % Patients achieving at least 50% of Max TotPar vs Tramadol at 48h

End point title	Multiple dose Phase - % Patients achieving at least 50% of Max TotPar vs Tramadol at 48h

End point description:

Percentage of patients achieving at least 50% of maximum Total Pain Relief (TOTPAR) at 48 h after the first dose in the Desketoprofen 25mg/Tramadol 75mg arm as compared with Tramadol 100mg arm (Multiple Dose Phase - Period 2)

End point type	Secondary

End point timeframe:

T=0 to T= 48h

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	190	192	45	38
Units: Percentage				
number (not applicable)	60	46.5	60	46.5

Statistical analyses

Statistical analysis title	Desketo Tramadol/Tramadol in PP Population

Statistical analysis description:

Multiple Dose Phase (Period 2) analysis

Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Tramadol 100 mg v Tramadol 100 mg v Desketoprofen 25mg/Tramadol 75mg
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	t-test, 2-sided

Secondary: Multiple dose Phase - % Patients achieving at least 50% of Max TotPar vs Tramadol at 72h

End point title	Multiple dose Phase - % Patients achieving at least 50% of Max TotPar vs Tramadol at 72h

End point description:

Percentage of patients achieving at least 50% of maximum Total Pain Relief (TOTPAR) at 72 h after the first dose in the Desketoprofen 25mg/Tramadol 75mg arm as compared with Tramadol 100mg arm (Multiple Dose Phase - Period 2)

End point type	Secondary

End point timeframe:

From T=0 to T=72h

End point values	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg	Desketoprofen 25mg/Tramadol 75mg	Tramadol 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	190	192	45	38
Units: Percentage				
number (not applicable)	62.6	53.5	62.6	53.5

Statistical analyses

Statistical analysis title	Desketo/Tramadol vs Tramadol in PP Population
Statistical analysis description: Multiple Dose Phase (Period 2) analysis	
Comparison groups	Desketoprofen 25mg/Tramadol 75mg v Tramadol 100 mg v Desketoprofen 25mg/Tramadol 75mg v Tramadol 100 mg
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Informed consent sing to final visit	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1
Reporting groups	
Reporting group title	Single Dose Phase - Period 1
Reporting group description: -	
Reporting group title	Multiple Dose Phase - Period 2
Reporting group description: -	

Serious adverse events	Single Dose Phase - Period 1	Multiple Dose Phase - Period 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 537 (0.19%)	1 / 538 (0.19%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0		
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 537 (0.19%)	0 / 538 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Single Dose Phase - Period 1	Multiple Dose Phase - Period 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 537 (11.92%)	143 / 538 (26.58%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	26 / 537 (4.84%)	33 / 538 (6.13%)	
occurrences (all)	26	33	
Somnolence			
subjects affected / exposed	11 / 537 (2.05%)	19 / 538 (3.53%)	
occurrences (all)	11	19	

Headache			
subjects affected / exposed	5 / 537 (0.93%)	13 / 538 (2.42%)	
occurrences (all)	5	13	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	19 / 537 (3.54%)	43 / 538 (7.99%)	
occurrences (all)	19	43	
Vomiting			
subjects affected / exposed	8 / 537 (1.49%)	35 / 538 (6.51%)	
occurrences (all)	8	35	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2021	The overall rationale for this amendment is to update the change in the sample size as per the re estimation of sample size and to incorporate the changes provided in erratum dated 19 May 2020. Main changes introduced: Downgrade of the Statistical Power from the original 90% to the actual 80% Reduction of the Sample size to 510 from original 680 patients Added examples of medications for clarification Creatinine clearance value defining abnormal renal function is corrected from ≥60 mL/min to ≤60 mL/min The number of countries where the study is conducted is reduced to 6 from 8; Italy and Lithuania are removed from the list.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported