



Clinical trial results:

A phase III, multicenter, randomized, parallel groups study to assess the efficacy and safety of 0,5 mg Tizaspray® administered intranasally versus Sirdalud® 2 mg tablets, in patients with acute low back pain

Summary

EudraCT number	2014-003040-12
Trial protocol	IT
Global end of trial date	20 September 2017

Results information

Result version number	v1 (current)
This version publication date	24 January 2018
First version publication date	24 January 2018
Summary attachment (see zip file)	TZSA2 - Clinical Trial Summary Report (TZSA2 - Clinical Trial Summary Report.pdf)

Trial information

Trial identification

Sponsor protocol code	TZSA2
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	MDM S.p.A.
Sponsor organisation address	Via Volturmo 29/b, Monza, Italy, 20052
Public contact	Servizio Segreteria MDM, MDM S.p.A., +39 039 3909110, mdm@mdmspa.com
Scientific contact	Servizio Segreteria MDM, MDM S.p.A., +39 039 3909110, mdm@mdmspa.com

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 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 September 2017
Global end of trial reached?	Yes
Global end of trial date	20 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1)To evaluate the muscle relaxant activity of Tizaspray 0.5 mg compared to Sirdalud 2 mg tablets as assessed by the "hand-to-floor" distance at baseline, day 3 and day 8.2)To evaluate the efficacy of Tizaspray 0.5 mg for the treatment of acute low back pain compared to Sirdalud 2 mg tablets as assessed by the Low Back Pain Intensity Scale (VAS) over maximum 7 days of treatment. 3)To evaluate the muscle relaxant activity of Tizaspray 0.5 mg compared to Sirdalud 2 mg tablets as assessed by the Schober test (positive/negative) at baseline, day 3 and day 8.

Protection of trial subjects:

A review of the safety surveillance database revealed cases of intentional and accidental tizanidine overdose. The clinical manifestations of tizanidine overdose were consistent with its known pharmacology. In the majority of cases a decrease in sensorium was observed including lethargy, somnolence, confusion and coma. Depressed cardiac function are also observed including most often bradycardia and hypotension. Respiratory depression is another common feature of tizanidine overdose. Should overdose occur, basic steps to ensure the adequacy of an airway and the monitoring of cardiovascular and respiratory systems should be undertaken. In general, symptoms resolve within one to three days following discontinuation of tizanidine and administration of appropriate therapy. Due to the similar mechanism of action, symptoms and management of tizanidine overdose are to those following clonidine overdose.

Patients experiencing somnolence, dizziness or any signs or symptoms of hypotension should refrain from activities requiring a high degree of alertness, e.g. driving a vehicle or operating machines. Caution is advised when Tizanidine is to be used with antihypertensives, including diuretics, since it may occasionally cause hypotension and bradycardia. In some patients rebound hypertension and tachycardia have been observed upon abrupt discontinuation of tizanidine when concomitantly used with antihypertensive drugs. In extreme cases, rebound hypertension might lead to cerebrovascular accident. Alcohol and sedatives may enhance the sedative action of tizanidine.

Patients were allowed to use the provided study Paracetamol for "rescue analgesia" for their low back pain. No

more than 6 tablets may be taken in a 24 hour period (doses separated by at least 4 hours).

The rescue medication was provided by the Sponsor in 500 mg tablets. The patient will be instructed to take tablets, possibly, on full stomach and to take the lowest number of possible tablets.

Background therapy:

Not applicable

Evidence for comparator:

Tizanidine HCl is the active substance of the medicinal product Sirdalud® tablets 2 mg, 4 mg, and 6 mg, marketed worldwide by Novartis Pharma since many years. Tizanidine HCl is a centrally acting skeletal muscle relaxant: it is an α_2 -adrenergic agonist structurally related to clonidine and acts mainly at spinal and supraspinal levels to inhibit excitatory interneurons. It is used for the symptomatic relief of spasticity associated with multiple sclerosis or with spinal cord injury or disease. It is also used in the symptomatic treatment of painful muscle spasm associated with musculoskeletal conditions.

The compound has got marketing approval in UK, USA, Canada, Italy, Japan, Belgium, Brazil, Denmark, Egypt, Finland, Germany, and Austria. In Italy the authorised indications are: painful muscle spasms related to static and functional diseases of spine (cervical and lumbar arthrosis syndromes, lumbago, torticollis) or following surgery (disc protusion, coxarthrosis); spasticity associated with neurological disorders (multiple sclerosis, chronic myelopathy, degenerative spinal disorders, stroke, etc.).

The physico-chemical properties of tizanidine, the pharmaceutical properties of tablets, the nonclinical pharmacology, toxicology, pharmacokinetics and metabolism and the clinical efficacy, safety, pharmacokinetics and metabolism are well understood.

Actual start date of recruitment	08 April 2015
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	Romania: 168
Country: Number of subjects enrolled	Italy: 68
Worldwide total number of subjects	236
EEA total number of subjects	236

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)	234
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients have been recruited between 8-Apr-2015 and 30-Jan-2017 in Italy (5 clinical sites) and Romania (5 clinical sites). The recruitment was competitive and only three clinical sites in Italy and four clinical sites in Romania have recruited some patients.

Pre-assignment

Screening details:

At Visit 1 (Day 1), prior to performing any trial assessments, the Investigator ensured that the patient had provided written informed consent. When screening procedures were performed, if eligible, the patient was immediately randomized and provided with the study treatment (first dose taken directly at site).

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The two treatments (Tizaspray and Sirdalud) had different formulations (nasal spray and oral tablets, respectively) and a double dummy technique was not applicable. Treatment was assigned as follows:
- Once eligibility is established (according to Inclusion/Exclusion Criteria), the Investigator had to enter the Electronic Case Report Form (e-CRF) and randomize the patient via web. The system indicated the kit number and the the type of treatment to assign to the patient.

Arms

Are arms mutually exclusive?	Yes
Arm title	TIZASPRAY

Arm description:

Patients treated with Tizaspray® nasal solution

Arm type	Experimental
Investigational medicinal product name	Tizaspray® nasal solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nasal spray, solution
Routes of administration	Inhalation use

Dosage and administration details:

8.169 mg/ml of tizanidine hydrochloride corresponding to 0.5 mg of tizanidine base/70 µL puff.
3 x 1 puff daily, intranasal administration.

Arm title	SIRDALUD
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Arm description:

Patients treated with Sirdalud® 2mg oral tablets

Arm type	Active comparator
Investigational medicinal product name	Sirdalud® 2mg oral tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2,29 mg/tablet of tizanidine hydrochloride corresponding to 2.0 mg of tizanidine base.
3 x 1 tablet daily, oral route.

Number of subjects in period 1	TIZASPRAY	SIRDALUD
Started	119	117
Completed	114	113
Not completed	5	4
Consent withdrawn by subject	4	1
Adverse event, non-fatal	-	2
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	TIZASPRAY
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Reporting group description:

Patients treated with Tizaspray® nasal solution

Reporting group title	SIRDALUD
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Reporting group description:

Patients treated with Sirdalud® 2mg oral tablets

Reporting group values	TIZASPRAY	SIRDALUD	Total
Number of subjects	119	117	236
Age categorical			
Units: Subjects			
Adults (18-64 years)	119	115	234
From 65-84 years	0	2	2
Gender categorical			
Units: Subjects			
Female	66	67	133
Male	53	50	103

Subject analysis sets

Subject analysis set title	Safety population Tizaspray
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Randomized patients taking at least one dose of Tizaspray

Subject analysis set title	Safety population Sirdalud
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Randomized patients taking at least one dose of Sirdalud

Subject analysis set title	ITT population Tizaspray
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

Patients randomly assigned to the Tizaspray group receiving at least one treatment dose and having at least one post-randomization assessment

Subject analysis set title	ITT population Sirdalud
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

Patients randomly assigned to the Sirdalud group receiving at least one treatment dose and having at least one post-randomization assessment

Subject analysis set title	PP population Tizaspray
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Subject analysis set type	Per protocol
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Subject analysis set description:

Patients randomized in the Tizaspray group with treatment compliance between 80%-130% inclusive, that had all post-randomization efficacy assessments and performed Visit 3 within the planned window (Day 8+2)

Subject analysis set title	PP population Sirdalud
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Subject analysis set type	Per protocol
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Subject analysis set description:

Patients randomized in the Sirdalud group with treatment compliance between 80%-130% inclusive, that had all post-randomization efficacy assessments and performed Visit 3 within the planned window (Day 8+2)

Reporting group values	Safety population Tizaspray	Safety population Sirdalud	ITT population Tizaspray
Number of subjects	118	116	115
Age categorical Units: Subjects			
Adults (18-64 years)	118	115	115
From 65-84 years	0	1	0
Gender categorical Units: Subjects			
Female	65	67	63
Male	53	49	52

Reporting group values	ITT population Sirdalud	PP population Tizaspray	PP population Sirdalud
Number of subjects	115	99	106
Age categorical Units: Subjects			
Adults (18-64 years)	114	99	106
From 65-84 years	1	0	0
Gender categorical Units: Subjects			
Female	67	53	62
Male	48	46	44

End points

End points reporting groups

Reporting group title	TIZASPRAY
Reporting group description: Patients treated with Tizaspray® nasal solution	
Reporting group title	SIRDALUD
Reporting group description: Patients treated with Sirdalud® 2mg oral tablets	
Subject analysis set title	Safety population Tizaspray
Subject analysis set type	Safety analysis
Subject analysis set description: Randomized patients taking at least one dose of Tizaspray	
Subject analysis set title	Safety population Sirdalud
Subject analysis set type	Safety analysis
Subject analysis set description: Randomized patients taking at least one dose of Sirdalud	
Subject analysis set title	ITT population Tizaspray
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Patients randomly assigned to the Tizaspray group receiving at least one treatment dose and having at least one post-randomization assessment	
Subject analysis set title	ITT population Sirdalud
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Patients randomly assigned to the Sirdalud group receiving at least one treatment dose and having at least one post-randomization assessment	
Subject analysis set title	PP population Tizaspray
Subject analysis set type	Per protocol
Subject analysis set description: Patients randomized in the Tizaspray group with treatment compliance between 80%-130% inclusive, that had all post-randomization efficacy assessments and performed Visit 3 within the planned window (Day 8+2)	
Subject analysis set title	PP population Sirdalud
Subject analysis set type	Per protocol
Subject analysis set description: Patients randomized in the Sirdalud group with treatment compliance between 80%-130% inclusive, that had all post-randomization efficacy assessments and performed Visit 3 within the planned window (Day 8+2)	

Primary: Changes in Hand-to-floor distance

End point title	Changes in Hand-to-floor distance
End point description: The changes in Hand-to-floor distance between Day 1 (baseline) and Day 8 (end of treatment) have been compared between treatment groups	
End point type	Primary
End point timeframe: Between Day 1 and Day 8	

End point values	TIZASPRAY	SIRDALUD	ITT population Tizaspray	ITT population Sirdalud
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	114	114	114	114
Units: cm				
arithmetic mean (standard deviation)	-15.51 (\pm 13.16)	-11.51 (\pm 12.64)	-15.51 (\pm 13.16)	-11.51 (\pm 12.64)

End point values	PP population Tizaspray	PP population Sirdalud		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	106		
Units: cm				
arithmetic mean (standard deviation)	-14.40 (\pm 11.33)	-10.95 (\pm 11.91)		

Attachments (see zip file)	Hand-to-floor - Differences from baseline (ITT)/F14020102.pdf
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Statistical analyses

Statistical analysis title	T-test on Hand-to-Floor Distance (ITT)
Statistical analysis description: T-test on changes between Day 1 and Day 8 in Hand-to-Floor Distance (ITT)	
Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0201 ^[1]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.37
upper limit	-0.63

Notes:

[1] - The difference between treatment groups was statistically significant at $p < 0.05$

Statistical analysis title	ANCOVA on Hand-to-Floor Distance (ITT)
Statistical analysis description: ANCOVA on changes between Day 1 and Day 8 in Hand-to-Floor Distance (ITT), with factors for treatment, site and baseline values	
Comparison groups	ITT population Tizaspray v ITT population Sirdalud

Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009 ^[2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.21
upper limit	-1.62

Notes:

[2] - The difference between treatment groups was statistically significant at $p < 0.001$

Statistical analysis title	T-test on Hand-to-Floor Distance (PP)
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Statistical analysis description:

T-test on changes between Day 1 and Day 8 in Hand-to-Floor Distance (PP)

Comparison groups	PP population Sirdalud v PP population Tizaspray
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0347 ^[3]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-3.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.66
upper limit	-0.25

Notes:

[3] - The difference between treatment groups was statistically significant at $p < 0.05$

Statistical analysis title	ANCOVA on Hand-to-Floor Distance (PP)
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Statistical analysis description:

ANCOVA on changes between Day 1 and Day 8 in Hand-to-Floor Distance (PP), with factors for treatment, site and baseline values

Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 ^[4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.47
upper limit	-2.03

Notes:

[4] - The difference between treatment groups was statistically significant at $p < 0.001$

Primary: Changes in Average Low Back Pain (VAS)

End point title	Changes in Average Low Back Pain (VAS)
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End point description:

End point type	Primary
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End point timeframe:

Between Day 1 and Day 8

End point values	TIZASPRAY	SIRDALUD	ITT population Tizaspray	ITT population Sirdalud
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	114	114	114	114
Units: mm				
arithmetic mean (standard deviation)	-44.96 (\pm 18.38)	-35.70 (\pm 20.81)	-44.96 (\pm 18.38)	-35.70 (\pm 20.81)

End point values	PP population Tizaspray	PP population Sirdalud		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	106		
Units: mm				
arithmetic mean (standard deviation)	-43.93 (\pm 17.44)	-35.19 (\pm 20.52)		

Attachments (see zip file)	Low back pain - Differences from baseline (ITT)/F14020104.pdf
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Statistical analyses

Statistical analysis title	T-test on Low back pain (ITT)
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Statistical analysis description:

T-test on changes in low back pain between Day 1 and Day 8 (ITT population)

Comparison groups	ITT population Tizaspray v ITT population Sirdalud
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Number of subjects included in analysis	228
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.0004 ^[5]
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Method	t-test, 2-sided
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Parameter estimate	Mean difference (final values)
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Point estimate	-9.26
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Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.39
upper limit	-4.14

Notes:

[5] - The difference between treatment groups was statistically significant at $p < 0.001$

Statistical analysis title	ANCOVA on Low back pain (ITT)
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Statistical analysis description:

ANCOVA on changes in low back pain between Day 1 and Day 8 (ITT population), with factors for treatment, site and baseline values

Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[6]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-8.92

Confidence interval

level	95 %
sides	2-sided
lower limit	-13.14
upper limit	-4.7

Notes:

[6] - The difference between treatment groups was statistically significant at $p < 0.001$

Statistical analysis title	T-test on Low back pain (PP)
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Statistical analysis description:

T-test on changes in low back pain between Day 1 and Day 8 (PP population)

Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	$= 0.0012$ ^[7]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-8.75

Confidence interval

level	95 %
sides	2-sided
lower limit	-14.01
upper limit	-3.49

Notes:

[7] - The difference between treatment groups was statistically significant at $p < 0.01$

Statistical analysis title	ANCOVA on Low back pain (PP)
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Statistical analysis description:

ANCOVA on changes in low back pain between Day 1 and Day 8 (PP population), with factors for

treatment, site and baseline values

Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[8]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-9.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.92
upper limit	-5.59

Notes:

[8] - The difference between treatment groups was statistically significant at $p < 0.001$

Primary: Positivity to Schober's test

End point title	Positivity to Schober's test
End point description:	
Patients with Schober's test higher than 5 mm were classified as positive, patients with higher Schober's test results were classified as negative. The number of patients with positive Schober's test was compared between treatment groups.	
End point type	Primary
End point timeframe:	
At Day 8 (+2)	

End point values	TIZASPRAY	SIRDALUD	ITT population Tizaspray	ITT population Sirdalud
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	114	114	114	114
Units: Patients positive to Schober's test	30	46	30	46

End point values	PP population Tizaspray	PP population Sirdalud		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	106		
Units: Patients positive to Schober's test	23	41		

Statistical analyses

Statistical analysis title	Chi-square test on Schober's test positivity (ITT)
Statistical analysis description:	
Chi-square test to assess the difference between treatment groups in the proportion of patients positive to Schober's test at Day 8 (ITT population)	

Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0246 ^[9]
Method	Chi-squared

Notes:

[9] - The difference between treatment groups was statistically significant at $p < 0.05$

Statistical analysis title	Logistic regression on Schober's test (ITT)
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Statistical analysis description:

Logistic regression to estimate OR (adjusted for site) between treatment groups for the proportion of patients positive to Schober's test at Day 8 (ITT population).

Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 ^[10]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.73

Notes:

[10] - The difference between treatment groups was statistically significant at $p < 0.01$

Statistical analysis title	Chi-square test on Schober's test positivity (PP)
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Statistical analysis description:

Chi-square test to assess the difference between treatment groups in the proportion of patients positive to Schober's test at Day 8 PP population)

Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0171 ^[11]
Method	Chi-squared

Notes:

[11] - The difference between treatment groups was statistically significant at $p < 0.05$

Statistical analysis title	Logistic regression on Schober's test (PP)
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Statistical analysis description:

Logistic regression to estimate OR (adjusted for site) between treatment groups for the proportion of patients positive to Schober's test at Day 8 (PP population)

Comparison groups	PP population Tizaspray v PP population Sirdalud
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Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0064 ^[12]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	0.73

Notes:

[12] - The difference between treatment groups was statistically significant at $p < 0.01$

Primary: Changes in Low Back Pain on movement by day

End point title	Changes in Low Back Pain on movement by day
End point description:	Low back Pain on movement was assessed daily by patient's questionnaire. The differences between Day 1 and each following day have been estimated and analyzed. The difference between treatment groups was statistically significant since Day 6 ($P < 0.01$). The analysis at Day 7 is reported here.
End point type	Primary
End point timeframe:	Between Day 1 and Day 7

End point values	TIZASPRAY	SIRDALUD	ITT population Tizaspray	ITT population Sirdalud
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	112	110	112	110
Units: mm				
arithmetic mean (standard deviation)	-40.96 (\pm 20.65)	-33.43 (\pm 22.82)	-40.96 (\pm 20.65)	-33.43 (\pm 22.82)

End point values	PP population Tizaspray	PP population Sirdalud		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	105		
Units: mm				
arithmetic mean (standard deviation)	-41.22 (\pm 20.37)	-33.12 (\pm 22.45)		

Attachments (see zip file)	Differences in Low back pain on moving by day(ITT)
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Statistical analyses

Statistical analysis title	T-Test on Low back pain (ITT)
Statistical analysis description: T-test on difference in low back pain between day 1 and day 7 (ITT population)	
Comparison groups	ITT population Sirdalud v ITT population Tizaspray
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0106 ^[13]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-7.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.28
upper limit	-1.77

Notes:

[13] - The difference between treatment groups was statistically significant at $p < 0.01667$

Statistical analysis title	ANCOVA on Low back pain (ITT)
Statistical analysis description: ANCOVA on difference in low back pain between day 1 and day 7, with factors for treatment, site and baseline values (ITT population)	
Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014 ^[14]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.66
upper limit	-2.85

Notes:

[14] - The difference between treatment groups was statistically significant at $p < 0.001$

Statistical analysis title	T-Test on Low back pain (PP)
Statistical analysis description: T-test on difference in low back pain between day 1 and day 7 (PP population)	
Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0078 ^[15]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-8.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.05
upper limit	-2.15

Notes:

[15] - The difference between treatment groups was statistically significant at $p < 0.01$

Statistical analysis title	ANCOVA on Low back pain (PP)
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Statistical analysis description:

ANCOVA on difference in low back pain between day 1 and day 7, with factors for treatment, site and baseline values (PP population)

Comparison groups	PP population Sirdalud v PP population Tizaspray
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 ^[16]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-9.31

Confidence interval

level	95 %
sides	2-sided
lower limit	-13.74
upper limit	-4.87

Notes:

[16] - The difference between treatment groups was statistically significant at $p < 0.001$

Primary: Changes in Low Back Pain at rest by day

End point title	Changes in Low Back Pain at rest by day
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End point description:

Low back Pain at rest was assessed daily by patient's questionnaire. The differences between Day 1 and each following day have been estimated and analyzed. The difference between treatment groups was statistically significant since Day 4 ($P < 0.05$). The analysis at Day 7 is reported here.

End point type	Primary
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End point timeframe:

Between day and day 7

End point values	TIZASPRAY	SIRDALUD	ITT population Tizaspray	ITT population Sirdalud
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	112	110	112	110
Units: mm				
arithmetic mean (standard deviation)	-40.69 (\pm 19.78)	-31.57 (\pm 21.94)	-40.69 (\pm 19.78)	-31.57 (\pm 21.94)

End point values	PP population Tizaspray	PP population Sirdalud		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	105		
Units: mm				
arithmetic mean (standard deviation)	-39.99 (\pm 19.55)	-31.55 (\pm 21.32)		

Attachments (see zip file)	Differences in Low back pain at rest by day (ITT)/F14020114.
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Statistical analyses

Statistical analysis title	T-test on Low back pain (ITT)
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Statistical analysis description:

T-test on low back pain at rest (ITT population)

Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0013 ^[17]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-9.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.64
upper limit	-3.59

Notes:

[17] - The difference between treatment groups was statistically significant at $p < 0.01$

Statistical analysis title	ANCOVA on Low back pain (ITT)
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Statistical analysis description:

ANCOVA on low back pain at rest (ITT population), with factors for treatment, site and baseline values

Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 ^[18]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.12
upper limit	-3.4

Notes:

[18] - The difference between treatment groups was statistically significant at $p < 0.001$

Statistical analysis title	T-test on Low back pain (PP)
Statistical analysis description: T-test on low back pain at rest (PP population)	
Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0037 ^[19]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-8.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.11
upper limit	-2.76

Notes:

[19] - The difference between treatment groups was statistically significant at $p < 0.01$

Statistical analysis title	ANCOVA on Low back pain (PP)
Statistical analysis description: ANCOVA on low back pain at rest (PP population), with factors for treatment, site and baseline values	
Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 ^[20]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-9.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.43
upper limit	-4.59

Notes:

[20] - The difference between treatment groups was statistically significant at $p < 0.001$

Primary: Changes in Low Back Pain when sleeping

End point title	Changes in Low Back Pain when sleeping
End point description: Low back Pain when sleeping was assessed daily by patient's questionnaire. The differences between Day 1 and each following day have been estimated and analyzed. The difference between treatment groups was statistically significant since Day 6 ($P < 0.01667$). The analysis at Day 7 is reported here.	
End point type	Primary
End point timeframe: Between day 1 and day 7	

End point values	TIZASPRAY	SIRDALUD	ITT population Tizaspray	ITT population Sirdalud
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	112	111	112	111
Units: mm				
arithmetic mean (standard deviation)	-37.14 (\pm 22.65)	-30.64 (\pm 20.74)	-37.14 (\pm 22.65)	-30.64 (\pm 20.74)

End point values	PP population Tizaspray	PP population Sirdalud		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	105		
Units: mm				
arithmetic mean (standard deviation)	-38.04 (\pm 22.36)	-29.77 (\pm 19.39)		

Attachments (see zip file)	Differences in Low back pain on sleep by day(ITT)/F14020116.
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Statistical analyses

Statistical analysis title	T-test on Low back pain (ITT)
Statistical analysis description: T-test on Low back pain (ITT population)	
Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0264 ^[21]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.24
upper limit	-0.77

Notes:

[21] - The difference between treatment groups was statistically significant at $p < 0.05$

Statistical analysis title	ANCOVA on Low back pain (ITT)
Statistical analysis description: ANCOVA on Low back pain (ITT population), with factors for treatment, site and baseline values	
Comparison groups	ITT population Tizaspray v ITT population Sirdalud

Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007 ^[22]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-7.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.58
upper limit	-3.41

Notes:

[22] - The difference between treatment groups was statistically significant at $p < 0.001$

Statistical analysis title	T-test on Low back pain (PP)
Statistical analysis description: T-test on Low back pain (PP population)	
Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0052 ^[23]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-8.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.04
upper limit	-2.5

Notes:

[23] - The difference between treatment groups was statistically significant at $p < 0.01$

Statistical analysis title	ANCOVA on Low back pain (PP)
Statistical analysis description: ANCOVA on Low back pain (PP population), with factors for treatment, site and baseline values	
Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[24]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-9.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.16
upper limit	-5.16

Notes:

[24] - The difference between treatment groups was statistically significant at $p < 0.001$

Secondary: Changes in Low Back Pain after 2nd dose (Day 1)

End point title	Changes in Low Back Pain after 2nd dose (Day 1)
End point description: Low back Pain was assessed after the second administration by patient's questionnaire. Low back pain was assessed at the moment of the second dose and after 30, 60, 90, 180 minutes. The differences between the moment of the second dose and after 30, 60, 90, 180 minutes have been estimated and analyzed. The difference between treatment groups was statistically significant after 30 and 60 minutes ($p < 0.01$), then the differences lowered. The analysis at 60 minutes is reported here.	
End point type	Secondary
End point timeframe: On day 1	

End point values	TIZASPRAY	SIRDALUD	ITT population Tizaspray	ITT population Sirdalud
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	109	106	109	106
Units: mm				
arithmetic mean (standard deviation)	-10.73 (\pm 11.72)	-7.16 (\pm 7.20)	-10.73 (\pm 11.72)	-7.16 (\pm 7.20)

End point values	PP population Tizaspray	PP population Sirdalud		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95	100		
Units: mm				
arithmetic mean (standard deviation)	-11.00 (\pm 11.37)	-7.19 (\pm 7.33)		

Attachments (see zip file)	Low back pain after 2nd dose (Day 1)/F14020202.pdf
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Statistical analyses

Statistical analysis title	T-test on Low back pain (ITT)
Statistical analysis description: T-test on Low back pain after second administration (ITT population)	
Comparison groups	ITT population Tizaspray v ITT population Sirdalud

Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority ^[25]
P-value	= 0.0078
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-3.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	-0.95

Notes:

[25] - The difference between treatment groups was statistically significant at $p < 0.01$

Statistical analysis title	ANCOVA on Low back pain (ITT)
Statistical analysis description: ANCOVA on Low back pain after second administration (ITT population), with factors for treatment, site and baseline values	
Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0117 ^[26]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.53
upper limit	-0.7

Notes:

[26] - The difference between treatment groups was statistically significant at $p < 0.01667$

Statistical analysis title	T-test on Low back pain (PP)
Statistical analysis description: T-test on Low back pain after second administration (PP population)	
Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0057 ^[27]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-3.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	-1.12

Notes:

[27] - The difference between treatment groups was statistically significant at $p < 0.01$

Statistical analysis title	ANCOVA on Low back pain (PP)
Statistical analysis description: ANCOVA on Low back pain after second administration (PP population), with factors for treatment, site and baseline values	
Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0085 [28]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.86
upper limit	-0.87

Notes:

[28] - The difference between treatment groups was statistically significant at $p < 0.01$

Secondary: Changes in Low Back Pain after 2nd dose (Day 2)

End point title	Changes in Low Back Pain after 2nd dose (Day 2)
End point description: The differences between the moment of the second dose and after 30, 60, 90, 180 minutes have been estimated and analyzed. The difference between treatment groups was statistically significant after 30 and 60 minutes ($p < 0.01$), then the differences lowered. The analysis at 60 minutes is reported here.	
End point type	Secondary
End point timeframe:	
On Day 2	

End point values	TIZASPRAY	SIRDALUD	ITT population Tizaspray	ITT population Sirdalud
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	113	112	113	112
Units: mm				
arithmetic mean (standard deviation)	-10.64 (\pm 12.53)	-7.07 (\pm 7.76)	-10.64 (\pm 12.53)	-7.07 (\pm 7.76)

End point values	PP population Tizaspray	PP population Sirdalud		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	105		
Units: mm				
arithmetic mean (standard deviation)	-11.63 (\pm	-7.32 (\pm 7.88)		

Attachments (see zip file)	Low back pain after 2nd dose (Day 2)/F14020204.pdf
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Statistical analyses

Statistical analysis title	T-test on Low back pain (ITT)
Statistical analysis description:	
T-test on low back pain after 2nd dose - Day 2 (ITT population)	
Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011 ^[29]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-3.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.31
upper limit	-0.82

Notes:

[29] - The difference between treatment groups was statistically significant at $p < 0.01667$

Statistical analysis title	ANCOVA on Low back pain (ITT)
Statistical analysis description:	
ANCOVA on low back pain after 2nd dose - Day 2 (ITT population), with factors for treatment, site and baseline values	
Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011 ^[30]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.91
upper limit	-0.77

Notes:

[30] - The difference between treatment groups was statistically significant at $p < 0.01667$

Statistical analysis title	T-test on Low back pain (PP)
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Statistical analysis description:

T-test on low back pain after 2nd dose - Day 2 (PPpopulation)

Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0037 ^[31]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.19
upper limit	-1.41

Notes:

[31] - The difference between treatment groups was statistically significant at $p < 0.01$

Statistical analysis title	ANCOVA on Low back pain (PP)
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Statistical analysis description:

ANCOVA on low back pain after 2nd dose - Day 2 (PP population), with factors for treatment, site and baseline values

Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0063 ^[32]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.44
upper limit	-1.07

Notes:

[32] - The difference between treatment groups was statistically significant at $p < 0.01$

Secondary: Changes in Low Back Pain after 2nd dose (Day 3)

End point title	Changes in Low Back Pain after 2nd dose (Day 3)
End point description: The differences between the moment of the second dose and after 30, 60, 90, 180 minutes have been estimated and analyzed. The difference between treatment groups was statistically significant after 30 and 60 minutes ($p < 0.05$), then the differences lowered. The analysis at 60 minutes is reported here.	
End point type	Secondary
End point timeframe: On day 3	

End point values	TIZASPRAY	SIRDALUD	ITT population Tizaspray	ITT population Sirdalud
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	113	111	113	111
Units: mm				
arithmetic mean (standard deviation)	-10.38 (\pm 10.04)	-7.51 (\pm 8.42)	-10.38 (\pm 10.04)	-7.51 (\pm 8.42)

End point values	PP population Tizaspray	PP population Sirdalud		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	105		
Units: mm				
arithmetic mean (standard deviation)	-11.31 (\pm 9.70)	-7.45 (\pm 8.43)		

Attachments (see zip file)	Low back pain after 2nd dose (Day 3)/F14020206.pdf
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Statistical analyses

Statistical analysis title	T-test on Low back pain (ITT)
Statistical analysis description:	
T-test on low back pain after 2nd dose - Day 3 (ITT population)	
Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0216 ^[33]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.31
upper limit	-0.43

Notes:

[33] - The difference between treatment groups was statistically significant at $p < 0.05$

Statistical analysis title	ANCOVA on Low back pain (ITT)
Statistical analysis description:	
ANCOVA on low back pain after 2nd dose - Day 3 (ITT population), with factors for treatment, site and baseline values	
Comparison groups	ITT population Tizaspray v ITT population Sirdalud

Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0166 ^[34]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3
upper limit	-0.54

Notes:

[34] - The difference between treatment groups was statistically significant at $p < 0.01667$

Statistical analysis title	T-test on Low back pain (PP)
Statistical analysis description:	
T-test on low back pain after 2nd dose - Day 3 (PP population)	
Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0027 ^[35]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-3.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.37
upper limit	-1.36

Notes:

[35] - The difference between treatment groups was statistically significant at $p < 0.01$

Statistical analysis title	ANCOVA on Low back pain (PP)
Statistical analysis description:	
ANCOVA on low back pain after 2nd dose - Day 3 (PP population), with factors for treatment, site and baseline values	
Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0035 ^[36]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.09
upper limit	-1.21

Notes:

[36] - The difference between treatment groups was statistically significant at $p < 0.01$

Secondary: Changes in Roland Disability Questionnaire

End point title	Changes in Roland Disability Questionnaire
End point description:	Changes in Roland Disability Questionnaire was administered between Day 1 and Day 8 have been estimated and compared between treatment groups.
End point type	Secondary
End point timeframe:	Between Day 1 and Day 8

End point values	TIZASPRAY	SIRDALUD	ITT population Tizaspray	ITT population Sirdalud
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	114	114	114	114
Units: points				
arithmetic mean (standard deviation)	-8.95 (\pm 4.31)	-6.79 (\pm 3.86)	-8.95 (\pm 4.31)	-6.79 (\pm 3.86)

End point values	PP population Tizaspray	PP population Sirdalud		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	106		
Units: points				
arithmetic mean (standard deviation)	-8.95 (\pm 4.15)	-6.88 (\pm 3.83)		

Attachments (see zip file)	Changes in Rolad Disability Questionnaire (ITT)/F14020208.pdf
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Statistical analyses

Statistical analysis title	T-test on RDQ (ITT)
Statistical analysis description:	T-test on Roland Disability Questionnaire (ITT population)
Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 ^[37]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.23
upper limit	-1.09

Notes:

[37] - The difference between treatment groups was statistically significant at $p < 0.001$

Statistical analysis title	ANCOVA on RDQ (ITT)
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Statistical analysis description:

ANCOVA on Roland Disability Questionnaire (ITT population), with factors for treatment, site and baseline values

Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[38]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.92

Confidence interval

level	95 %
sides	2-sided
lower limit	-2.75
upper limit	-1.09

Notes:

[38] - The difference between treatment groups was statistically significant at $p < 0.001$

Statistical analysis title	T-test on RDQ (PP)
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Statistical analysis description:

T-test on Roland Disability Questionnaire (PP population)

Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	$= 0.0003$ ^[39]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.07

Confidence interval

level	95 %
sides	2-sided
lower limit	-3.17
upper limit	-0.97

Notes:

[39] - The difference between treatment groups was statistically significant at $p < 0.001$

Statistical analysis title	ANCOVA on RDQ (PP)
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Statistical analysis description:

ANCOVA on Roland Disability Questionnaire (PP population), with factors for treatment, site and baseline

values

Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[40]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.75
upper limit	-1.13

Notes:

[40] - The difference between treatment groups was statistically significant at $p < 0.001$

Secondary: Changes in Schober's test

End point title	Changes in Schober's test
End point description:	
Schober test difference in cm between day 1 and day 8	
End point type	Secondary
End point timeframe:	
Between Day 1 and Day 8	

End point values	TIZASPRAY	SIRDALUD	ITT population Tizaspray	ITT population Sirdalud
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	114	114	114	114
Units: cm				
arithmetic mean (standard deviation)	2.82 (\pm 1.55)	2.01 (\pm 2.00)	2.82 (\pm 1.55)	2.01 (\pm 2.00)

End point values	PP population Tizaspray	PP population Sirdalud		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99	106		
Units: cm				
arithmetic mean (standard deviation)	2.90 (\pm 1.56)	2.02 (\pm 1.34)		

Attachments (see zip file)	Changes in Schober test (ITT)/F14020118.pdf
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Statistical analyses

Statistical analysis title	T-test on Schober's test (ITT)
Statistical analysis description: T-test on Schober's test (ITT population)	
Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[41]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.19

Notes:

[41] - The difference between treatment groups was statistically significant at $p < 0.001$

Statistical analysis title	ANCOVA on Schober's test (ITT)
Statistical analysis description: ANCOVA on Schober's test (ITT population), with factors for treatment, site and baseline values	
Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[42]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.08

Notes:

[42] - The difference between treatment groups was statistically significant at $p < 0.001$

Statistical analysis title	T-test on Schober's test (PP)
Statistical analysis description: T-test on Schober's test (PP population)	
Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[43]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.88

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.28

Notes:

[43] - The difference between treatment groups was statistically significant at $p < 0.001$

Statistical analysis title	ANCOVA on Schober's test (PP)
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Statistical analysis description:

ANCOVA on Schober's test (PP population), with factors for treatment, site and baseline values

Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [44]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.1

Notes:

[44] - The difference between treatment groups was statistically significant at $p < 0.001$

Secondary: Number of patients taking paracetamol tablets

End point title	Number of patients taking paracetamol tablets
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End point description:

The number of patients that have taken paracetamol tablets during the study was compared between treatment groups

End point type	Secondary
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End point timeframe:

Between Day 1 and Day 8

End point values	TIZASPRAY	SIRDALUD	ITT population Tizaspray	ITT population Sirdalud
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	112	113	112	113
Units: tablets	67	79	67	79

End point values	PP population Tizaspray	PP population Sirdalud		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	104		

Units: tablets	59	72		
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Statistical analyses

Statistical analysis title	Chi-square test on patients took paracetamol (ITT)
Statistical analysis description: Chi-square test on the number of patients that have taken any paracetamol tablets during the study (ITT)	
Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1129 ^[45]
Method	Chi-squared

Notes:

[45] - The difference between treatment groups was not statistically significant

Statistical analysis title	Logistic reg. on patients took paracetamol (ITT)
Statistical analysis description: Logistic regression on the number of patients that have taken any paracetamol tablets during the study (ITT), with factors for treatment and site	
Comparison groups	ITT population Tizaspray v ITT population Sirdalud
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0678 ^[46]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.04

Notes:

[46] - The difference between treatment groups was not statistically significant

Statistical analysis title	Chi-square test on patients took paracetamol (PP)
Statistical analysis description: Chi-square test on the number of patients that have taken any paracetamol tablets during the study (PP)	
Comparison groups	PP population Tizaspray v PP population Sirdalud

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1793 ^[47]
Method	Chi-squared

Notes:

[47] - The difference between treatment groups was not statistically significant

Statistical analysis title	Logistic reg. on patients took paracetamol (PP)
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Statistical analysis description:

Logistic regression on the number of patients that have taken any paracetamol tablets during the study (PP), with factors for treatment and site

Comparison groups	PP population Tizaspray v PP population Sirdalud
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1083 ^[48]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	1.12

Notes:

[48] - The difference between treatment groups was not statistically significant

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Between Day 1 (Baseline) and Day 8 (end of treatment/end of study)

Adverse event reporting additional description:

The reporting period for AEs was the period between the time of Informed Consent signature and day 8 (+2). At the end of this follow-up period, all unresolved AEs were documented on the CRF as "ongoing".

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	TIZASPRAY
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Reporting group description:

Patients treated with Tizaspray® nasal solution

Reporting group title	SIRDALUD
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Reporting group description:

Patients treated with Sirdalud® 2mg oral tablets

Serious adverse events	TIZASPRAY	SIRDALUD	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 118 (0.00%)	0 / 116 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	TIZASPRAY	SIRDALUD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 118 (10.17%)	6 / 116 (5.17%)	
Vascular disorders			
Dizziness			
subjects affected / exposed	2 / 118 (1.69%)	1 / 116 (0.86%)	
occurrences (all)	2	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 118 (0.85%)	0 / 116 (0.00%)	
occurrences (all)	1	0	
Headache			

subjects affected / exposed occurrences (all)	1 / 118 (0.85%) 1	1 / 116 (0.86%) 1	
Somnolence subjects affected / exposed occurrences (all)	3 / 118 (2.54%) 3	3 / 116 (2.59%) 3	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	0 / 118 (0.00%) 0	1 / 116 (0.86%) 1	
Burning sensation subjects affected / exposed occurrences (all)	1 / 118 (0.85%) 1	0 / 116 (0.00%) 0	
Fatigue subjects affected / exposed occurrences (all)	0 / 118 (0.00%) 0	1 / 116 (0.86%) 1	
Gastrointestinal disorders			
Aphthous ulcer subjects affected / exposed occurrences (all)	1 / 118 (0.85%) 1	0 / 116 (0.00%) 0	
Dry mouth subjects affected / exposed occurrences (all)	1 / 118 (0.85%) 1	2 / 116 (1.72%) 2	
Nausea subjects affected / exposed occurrences (all)	1 / 118 (0.85%) 1	0 / 116 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Nasal discomfort subjects affected / exposed occurrences (all)	1 / 118 (0.85%) 3	0 / 116 (0.00%) 0	
Nasal pruritus subjects affected / exposed occurrences (all)	2 / 118 (1.69%) 6	0 / 116 (0.00%) 0	
Psychiatric disorders			
Disturbance in attention subjects affected / exposed occurrences (all)	0 / 118 (0.00%) 0	1 / 116 (0.86%) 1	

Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 118 (0.85%)	0 / 116 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 May 2015	The amendment no. 2 to the Protocol concerned the changes of some eligibility criteria, in particular Exclusion Criterion No.13 and Inclusion Criterion No. 4, modified also taking into account the opinion of the Italian Investigators.
09 December 2015	The Amendment no. 3 was aimed at reducing the blood tests from 2 to just 1, maintaining only the baseline blood draw.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported