Clinical trial results:
A randomized double blind placebo controlled multicenter study to assess the efficacy and tolerability of tolperisone as add on treatment with standardized NSAID of acute non specific low back pain.

Summary

EudraCT number	2021-006042-13
Trial protocol	HU
Global end of trial date	03 February 2023

Results information

Result version number	v1 (current)
This version publication date	18 February 2024
First version publication date	18 February 2024

Trial information

Trial identification

Sponsor protocol code	MEDI-TOLP-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	MEDITOP Pharmaceutical Ltd.
Sponsor organisation address	Ady Endre utca 1., Pilisborosjenő, Hungary, 2097
Public contact	Dr. Orsolya Czifra Phone: (+36) 30 789 20 85 orsolya.czifra@meditop.hu info@meditop.hu, Medical Director, 36 307892085, info@meditop.hu
Scientific contact	Dr. Orsolya Czifra, Medical Director, 36 307892085, orsolya.czifra@meditop.hu

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	14 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 November 2022
Global end of trial reached?	Yes
Global end of trial date	03 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether tolperisone, when administered with standardized NSAID treatment to patients with acute non-specific low back pain is effective in reducing pain.

Protection of trial subjects:

This study was conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The investigator or his/her representative explained the nature of the study to the participant and answered all questions regarding the study during the screening visit. Patients were handed over a detailed Information Leaflet (PIL) about the study.

Participants were informed that their participation is voluntary. Participants were required to sign a statement of informed consent ICF approved by the Central Ethical Committee (CEC).
The patients' medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized physician obtaining the informed consent must also sign the ICF.
Participants were consented to the most current version of the ICF(s) during their participation in the study.

Background therapy:

Every enrolled patient received standardized oral ibuprofen treatment (ie. Algoflex Rapid 3x400 mg daily for 14 days).

Evidence for comparator:

Placebo was used as a comparator during the study.

Actual start date of recruitment	06 April 2022
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hungary: 331
Worldwide total number of subjects	331
EEA total number of subjects	331

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)	331
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male and female patients between the ages 18-55 years with muscle spasm associated with acute non-specific low back pain were enrolled in the study.

Pre-assignment

Screening details:

All screening evaluations were completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigators maintained a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
Screening and randomisation were completed on the

Period 1

Period 1 title	Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

This was a double blind, placebo controlled study, both the investigators and patients were blind to study treatment. Patients received either placebo or active (matching) per os treatment. Unblinding for medical emergency in which the knowledge of the specific blinded study treatment would affect the immediate management of the participant’s condition was available for all investigators.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active

Arm description:

Patients received 3x150 mg tolperison (IMP) and a standard 3x400 mg ibuprophen for 14 days.

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

Dosage and administration details:

3x1 tablets/day. 1 tablet contained 150 mg tolperisone.
To be consumed after meal with a glass of water.
Every enrolled patient received standardized oral ibuprofen treatment (ie. Algoflex Rapid 3x400 mg daily for 14 days).
In addition to the standardized ibuprofen baseline therapy the patients received additional ibuprofen as rescue medication. Maximum dose of ibuprofen was not to exceed 2400 mg/day (3x800 mg).

Arm title	Placebo

Arm description:

Patients received 3x150 mg placebo (IMP) and a standard 3x400 mg ibuprophen for 14 days.

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

Dosage and administration details:

Patients received 3x150 mg placebo (IMP) and a standard 3x400 mg ibuprophen for 14 days.
Medication was to be taken after meal, with a glass of water.
Every patient received standardized ibuprophen therapy (3*400 mg) and additional ibuprophen as rescue medication (up to 3*800 mg maximum).

Number of subjects in period 1	Active	Placebo
Started	165	166
Completed	164	166
Not completed	1	0
Lost to follow-up	1	-

Period 2

Period 2 title	Follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Treatment blinding was kept until database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Active	Placebo
Started	164	166
Completed	164	165
Not completed	0	1
Sponsor's decision	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Active
Reporting group description:	
Patients received 3x150 mg tolperison (IMP) and a standard 3x400 mg ibuprophen for 14 days.	
Reporting group title	Placebo
Reporting group description:	
Patients received 3x150 mg placebo (IMP) and a standard 3x400 mg ibuprophen for 14 days.	

Reporting group values	Active	Placebo	Total
Number of subjects	165	166	331
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age ranged from 18 to 66 years.			
Units: years			
arithmetic mean	40.6	40.8	
standard deviation	± 10.4	± 10.3	-
Gender categorical			
Male/Female			
Units: Subjects			
Female	104	82	186
Male	61	84	145
Spasticity			
Muscle spasticity of the low back pain region assessed during physical examination by the investigator.			
Units: Subjects			
0=no spasticity	0	0	0
1=slight muscle spasm	0	0	0
2=moderate muscle spasm	140	142	282
3=severe muscle spasm	25	24	49
Height			
height at baseline			
Units: cm			
arithmetic mean	170.9	171.7	
standard deviation	± 9.6	± 9.5	-
Weight			
Patient body weight at baseline			

Units: kg			
arithmetic mean	78.5	80.7	
standard deviation	± 16	± 16.1	-
BMI			
Body Mass Index			
Units: kg/m2			
arithmetic mean	26.7	27.2	
standard deviation	± 4.2	± 4.3	-

End points

End points reporting groups

Reporting group title	Active
Reporting group description:	
Patients received 3x150 mg tolperison (IMP) and a standard 3x400 mg ibuprophen for 14 days.	
Reporting group title	Placebo
Reporting group description:	
Patients received 3x150 mg placebo (IMP) and a standard 3x400 mg ibuprophen for 14 days.	
Reporting group title	Active
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population is defined as all subjects who were exposed to study treatment, regardless of the duration of therapy.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients in Safety Population who have primary efficacy data.	
Subject analysis set title	Per Protocol Set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
All FAS patients who finished the study according to the protocol and had no major protocol deviations. In case of efficacy analyses the definition of estimands include the exact definition of the study population that is used for the given analysis.	

Primary: Change in VAS pain score

End point title	Change in VAS pain score
End point description:	
The change in pain visual analogue scale (VAS) score (pain on movement) from Baseline to Day 5.	
End point type	Primary
End point timeframe:	
Baseline to Day 5	

End point values	Active	Placebo	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	164	166	330	
Units: cm				
arithmetic mean (standard deviation)	-2.34 (± 1.903)	-2.44 (± 1.963)	-2.39 (± 1.931)	

Statistical analyses

Statistical analysis title	Mixed model comparisons – VAS pain on movement up

Statistical analysis description:

Pain on movement
Mixed model results of the treatment difference
Active vs Placebo
While on treatment strategy

Comparison groups	Active v Placebo
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.3371 [2]
Method	Mixed models analysis
Parameter estimate	LS mean
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	0.08
Variability estimate	Standard deviation
Dispersion value	1.931

Notes:

[1] - Mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available at Day 3 and Day 5 were used until the start of the use of any prohibited medications. Missing data was accounted for by the MMRM model. Fixed effects: treatment, time point, treatment by time point interaction; and baseline VAS value. The point estimate for the least-squares mean of the treatment difference at Day 5 and the corresponding 95% confidence interval and p-value were summarized.
[2] - Treatment*day

Secondary: FFD

End point title	FFD

End point description:

The change in Finger-to-Floor Distance (FFD) from Baseline throughout the study (Day 3, 5, 7 and 14).

End point type	Secondary

End point timeframe:

Baselin to Day 14.

End point values	Active	Placebo	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	163	165	328	
Units: cm				
arithmetic mean (standard deviation)	-11.03 (± 13.008)	-10.44 (± 10.727)	-10.74 (± 11.901)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lumbar Spine Side Flexion test

End point title	Lumbar Spine Side Flexion test

End point description:

The change in the result of Lumbar Spine Side Flexion test from Baseline throughout the study (Day 3, 5, 7 and 14).

End point type	Secondary

End point timeframe:

From Baseline to Day 14.

End point values	Active	Placebo	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	163	165	328	
Units: cm				
arithmetic mean (standard deviation)	-6.45 (± 6.732)	-6.02 (± 5.801)	-6.23 (± 6.275)	

Statistical analyses

No statistical analyses for this end point

Secondary: RMDQ

End point title	RMDQ

End point description:

The change in Roland-Morris Disability Questionnaire (RMDQ) score from Baseline throughout the study (Day 3, 5, 7 and 14).

End point type	Secondary

End point timeframe:

From Baseline to Day 14

End point values	Active	Placebo	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	164	166	330	
Units: points				
arithmetic mean (standard deviation)	-5.17 (± 4.295)	-5.63 (± 3.918)	-5.4 (± 4.11)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pain VAS diary

End point title	Pain VAS diary

End point description:

The change in pain VAS scores (pain at rest) from Baseline throughout the study assessed by the patient daily in the Patient Diary.

End point type	Secondary

End point timeframe:

From Baseline to Day 14

End point values	Active	Placebo	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	148	155	303	
Units: cm				
arithmetic mean (standard deviation)	-3.9 (± 2.562)	-3.95 (± 2.709)	-3.93 (± 2.633)	

Statistical analyses

No statistical analyses for this end point

Secondary: Sum of Pain Intensity Differences

End point title	Sum of Pain Intensity Differences

End point description:

The Sum of Pain Intensity Differences (SPID): the area under the time-analgesic effect curve for pain intensity from baseline to Day 3, 5, 7 and 14.

End point type	Secondary

End point timeframe:

Baseline to Day 14

End point values	Active	Placebo	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	163	165	328	
Units: cm				
arithmetic mean (standard deviation)	79.09 (± 21.785)	74.99 (± 24.448)	77.03 (± 23.219)	

Statistical analyses

No statistical analyses for this end point

Secondary: Rescue medication

End point title	Rescue medication

End point description:

The amount of rescue medication taken by the patient and recorded in the patient diary.

End point type	Secondary

End point timeframe:

Baseline to Day 14

End point values	Active	Placebo	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	164	166	330	
Units: tablet				
arithmetic mean (standard deviation)	3.64 (± 5.85)	3.22 (± 7.081)	3.43 (± 6.492)	

Statistical analyses

No statistical analyses for this end point

Secondary: Physician’s global assessment of the treatment

End point title	Physician’s global assessment of the treatment

End point description:

The value of physician’s global assessment of the treatment (PhGA) throughout the study (Day 3, 5, 7 and 14).

End point type	Secondary

End point timeframe:

Baseline to DAy 14

End point values	Active	Placebo	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	164	166	330	
Units: points				
poor	9	6	15	
fair	17	21	38	
good	60	52	112	
very good	58	60	118	
excellent	18	26	44	

Statistical analyses

No statistical analyses for this end point

Secondary: Patient’s Global Impression of improvement

End point title	Patient’s Global Impression of improvement

End point description:

The value of Patient’s Global Impression of improvement (PGIC-I)

End point type	Secondary

End point timeframe:

Baseline to Day 14

End point values	Active	Placebo	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	164	166	330	
Units: patients				
poor	9	4	13	
fair	19	23	42	
good	46	51	97	
very good	67	57	124	
excellent	21	30	51	

Statistical analyses

No statistical analyses for this end point

Secondary: Responder rate

End point title	Responder rate

End point description:

Responder rate at Day 3, 5, 7 and 14. A patient is considered responder if the absolute change in VAS score from baseline is >=3.5 cm.

End point type	Secondary

End point timeframe:

Day 3-14

End point values	Active	Placebo	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	165	166	331	
Units: patients				
responder	116	120	236	
not-responder	47	45	92	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: EQ-5D

End point title	EQ-5D

End point description:

The change in quality of life (EQ-5D) scores from Baseline throughout the study (Day 3, 5, 7 and 14).

End point type	Other pre-specified

End point timeframe:

Baseline to Day 14

End point values	Active	Placebo	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	163	165	328	
Units: points				
arithmetic mean (standard deviation)	6.83 (± 1.884)	6.73 (± 1.997)	6.78 (± 1.94)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Days of absenteeism

End point title	Days of absenteeism

End point description:

Days of absenteeism from work from Baseline to Day 14.

End point type	Other pre-specified

End point timeframe:

Baseline to Day 14

End point values	Active	Placebo	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	149	144	293	
Units: days	26	311	57	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of recurrences

End point title	Number of recurrences

End point description:

Number of recurrences until the 3 months follow-up visit.

End point type	Other pre-specified

End point timeframe:

3 months

End point values	Active	Placebo	Full analysis set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	164	165	329	
Units: number	24	20	44	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All SAEs and AEs were collected from the start of treatment until the follow-up (D21) visit.

Adverse event reporting additional description:

The following events were considered AESI and immediately reported to the Sponsor (same procedure as SAE):
Hypersensitivity reactions (regardless of severity)
• Any observed or reported hypersensitivity reaction will be closely monitored by the Investigators until resolution.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26

Reporting groups

Reporting group title	Active

Reporting group description:

Patients receiving Tolperisone treatment

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Active	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 165 (0.00%)	0 / 166 (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: 0.05 %

Non-serious adverse events	Active	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 165 (16.97%)	23 / 166 (13.86%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 165 (0.61%)	1 / 166 (0.60%)	
occurrences (all)	1	1	
Surgical and medical procedures			
Ear operation			

subjects affected / exposed	0 / 165 (0.00%)	1 / 166 (0.60%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 165 (0.61%)	0 / 166 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 165 (1.21%)	1 / 166 (0.60%)	
occurrences (all)	2	1	
Blood bilirubin increased			
subjects affected / exposed	1 / 165 (0.61%)	0 / 166 (0.00%)	
occurrences (all)	1	0	
Blood glucose increased			
subjects affected / exposed	1 / 165 (0.61%)	0 / 166 (0.00%)	
occurrences (all)	1	0	
Blood urine present			
subjects affected / exposed	0 / 165 (0.00%)	1 / 166 (0.60%)	
occurrences (all)	0	1	
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 165 (0.00%)	1 / 166 (0.60%)	
occurrences (all)	0	1	
Platelet count decreased			
subjects affected / exposed	1 / 165 (0.61%)	1 / 166 (0.60%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 165 (0.00%)	1 / 166 (0.60%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 165 (0.61%)	0 / 166 (0.00%)	
occurrences (all)	1	0	
Ventricular extrasystoles			
subjects affected / exposed	0 / 165 (0.00%)	1 / 166 (0.60%)	
occurrences (all)	0	1	

Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 165 (0.61%)	0 / 166 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	5 / 165 (3.03%)	4 / 166 (2.41%)	
occurrences (all)	5	4	
Nerve compression			
subjects affected / exposed	1 / 165 (0.61%)	0 / 166 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	0 / 165 (0.00%)	1 / 166 (0.60%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 166 (0.00%)	
occurrences (all)	1	0	
Lymphadenopathy			
subjects affected / exposed	0 / 165 (0.00%)	1 / 166 (0.60%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 165 (1.21%)	0 / 166 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 165 (1.21%)	3 / 166 (1.81%)	
occurrences (all)	2	3	
Diarrhoea			
subjects affected / exposed	1 / 165 (0.61%)	4 / 166 (2.41%)	
occurrences (all)	1	4	
Dry mouth			
subjects affected / exposed	1 / 165 (0.61%)	0 / 166 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	3 / 165 (1.82%)	1 / 166 (0.60%)	
occurrences (all)	3	1	

Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 165 (0.61%)	1 / 166 (0.60%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	0 / 165 (0.00%)	1 / 166 (0.60%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 165 (1.82%)	3 / 166 (1.81%)	
occurrences (all)	3	3	
Muscle spasms			
subjects affected / exposed	1 / 165 (0.61%)	0 / 166 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	0 / 165 (0.00%)	1 / 166 (0.60%)	
occurrences (all)	0	1	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 165 (0.61%)	1 / 166 (0.60%)	
occurrences (all)	1	1	
Herpes zoster			
subjects affected / exposed	1 / 165 (0.61%)	0 / 166 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	2 / 165 (1.21%)	1 / 166 (0.60%)	
occurrences (all)	2	1	
Otitis externa			
subjects affected / exposed	0 / 165 (0.00%)	1 / 166 (0.60%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 165 (0.00%)	1 / 166 (0.60%)	
occurrences (all)	0	1	
Tonsillitis			

subjects affected / exposed	0 / 165 (0.00%)	1 / 166 (0.60%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 165 (0.61%)	0 / 166 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported