



Clinical trial results:

Title: A Phase 2, Open-Label 20-Week Study to Evaluate the Safety and Efficacy of Setmelanotide in Subjects with Hypothalamic Obesity.

Trial design: This was a Phase 2, multicentre, open-label, proof of concept study designed to assess the effect of setmelanotide on weight in individuals affected by hypothalamic obesity (HO). It was planned to enrol approximately 15 patients with HO, aged 6 to 40 years, across 3-5 clinical sites in the US. HO is caused by hypothalamic insults (eg, tumours, tumour resections, radiotherapy treatment) that may result in defective leptin signalling (the MC3/4 receptor pathway). The study consisted of a 2-8 week screening period and a 16-week treatment period.

After enrolment, patients entered the screening period when they completed a daily hunger questionnaire. During the treatment period, all patients initiated treatment with subcutaneous (SC) setmelanotide and the dose was to be escalated to a final dose of 3.0 mg once daily (QD) (the therapeutic dose). Patients were to continue dosing at 3.0 mg QD and return to the clinic every 4 weeks (at Visits 3-5) to complete all study assessments. Note, doses of <3.0 mg QD could be administered if needed due to an adverse event or other safety or tolerability concern. After 16 weeks, at Visit 6, the patient received the last setmelanotide injection and participation in the study concluded in one of the following 2 ways:

- Completed Visit 6 and enrolled in a separate extension study, Rhythm Study RM-493-022.
- Decided not to participate in the extension study and proceeded to the End-of-Study (EOS) visit (Visit 7) at Week 20 for a final safety review.

The median duration of treatment was 16.14 weeks (range: 7.43 to 22.57 weeks).

The primary endpoint was defined as the proportion of patients who achieved at least 5% body mass index (BMI) reduction from baseline at ~16 weeks of treatment with setmelanotide.

Summary

EudraCT number	2022-004107-32
Trial protocol	Outside EU/EEA
Global end of trial date	28 June 2022

Results information

Result version number	v1 (current)
This version publication date	27 April 2023
First version publication date	27 April 2023

Trial information

Trial identification

Sponsor protocol code	RM-493-030
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04725240
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rhythm Pharmaceuticals, Inc,
Sponsor organisation address	222 Berkeley Street, 12th Floor, Boston, United States, MA 02116
Public contact	Clinical Trial Information Desk, Rhythm Pharmaceuticals, Inc., +1 857-264-4280, clinicaltrials@rhythmtx.com
Scientific contact	Clinical Trial Information Desk, Rhythm Pharmaceuticals, Inc., +1 857-264-4280, clinicaltrials@rhythmtx.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 June 2022
Global end of trial reached?	Yes
Global end of trial date	28 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the change in body weight in response to setmelanotide administered subcutaneously (SC) daily in patients with HO.

Protection of trial subjects:

The Institutional Review Board (IRB) reviewed all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study was only conducted at sites where IRB/IEC approval had been obtained.

This study was conducted in accordance with:

- Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- The International Council for Harmonisation (ICH) Good Clinical Practices (GCP) Guideline [E6]
- Applicable laws and regulatory requirements.

After the study had been fully explained, written informed consent was obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent complied with ICH-GCP and all applicable regulatory requirement(s).

Background therapy:

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) received at the time of enrolment or received during the study had to be recorded. The Medical Monitor was to be contacted with any questions regarding concomitant or prior therapy.

However, patients were not permitted to enter the study if they have had weight gain >5% during the previous 3 months or >2% weight loss during the prior 3 months. Dietary and/or exercise regimens, with or without the use of medications, supplements or herbal treatments associated with weight loss (eg, orlistat, lorcaserin, phentermine, topiramate, naltrexone, bupropion, GLP1 receptor agonists, etc.) were allowed if:

- the regimen and/or dose had been stable for at least 3 months prior to randomisation
- the patient had not experienced weight loss $\geq 2\%$ during the previous 3 months, AND
- the patient intended to keep the regimen and/or dose stable throughout the course of the study.

GLP 1 receptor agonists could be used up to the dose approved for the treatment of diabetes mellitus (eg, liraglutide up to a daily dose of 1.8 mg) as long as (1) it was not being prescribed for the treatment of obesity, (2) the dose had been stable for at least 3 months prior to enrolment, (3) the patient had not experienced >3% weight loss during the previous 3 months, AND (4) the patient intended to keep the dose stable throughout the course of the study.

Other medications that could have caused weight loss were allowed as long as the patient (1) had used a stable dose for at least 3 months prior to enrolment, (2) had not lost weight during the previous 3 months, and (3) intended to keep the dose stable through the course of the study.

All concomitant medications had to be kept at a stable dose throughout the course of the study, unless a dose change was necessary to treat an AE.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	06 June 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	18
EEA total number of subjects	0

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)	5
Adolescents (12-17 years)	8
Adults (18-64 years)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study recruited 18 patients with HO in 5 clinical sites in the United States with the first patient enrolled on 06 June 2021 (first dosed 12 July 2021) and the last patient visit on 28 June 2022. Patients were included if they had documented evidence of HO.

Pre-assignment

Screening details:

Screening assessments included medical history, physical exam, comprehensive skin examination, laboratory tests, blood pressure, hunger scale, body composition, Columbia-Suicide Severity Rating Scale (C-SSRS) form, and energy expenditure evaluation.

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label, proof-of-concept study.

Arms

Arm title	All patients
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Arm description:

All patients with HO included in the study.

Arm type	Experimental
Investigational medicinal product name	Setmelanotide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Setmelanotide was administered once daily (QD) via SC injection. The therapeutic dose was 3.0 mg QD, which was achieved after dose titration. No dose >3.0 mg QD was to be administered. However, doses <3.0 mg QD could be administered, after consultation with the Sponsor, if necessary due to an AE or other safety or tolerability concern. The standard dose escalation was:

Patients aged 6 to <16 years: 1.0 mg in Weeks 1-2, 2.0 mg in Weeks 3-4, and 3.0 mg in Weeks 5-16.

Patients aged ≥16 years: 2.0 mg in Weeks 1-2, and 3.0 mg in Weeks 3-16.

Number of subjects in period 1	All patients
Started	18
Completed	16
Not completed	2
Adverse event, non-fatal	2

Baseline characteristics

Reporting groups

Reporting group title	All patients
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Reporting group description:

All patients with HO included in the study.

Reporting group values	All patients	Total	
Number of subjects	18	18	
Age categorical			
Units: Subjects			
< 18	13	13	
>= 18	5	5	
Age continuous			
Units: years			
arithmetic mean	15.0		
standard deviation	± 5.30	-	
Gender categorical			
Units: Subjects			
Female	7	7	
Male	11	11	
Weight at baseline			
The most recent weight measurement prior to the first administration of study drug.			
Units: kilogram(s)			
arithmetic mean	102.76		
standard deviation	± 30.120	-	
BMI at baseline			
The most recent body mass index (BMI) measurement prior to the first administration of study drug.			
Units: kg/m2			
arithmetic mean	37.95		
standard deviation	± 6.532	-	
Waist circumference at baseline			
The most recent waist circumference measurement prior to the first administration of study drug.			
Units: centimetre			
arithmetic mean	114.07		
standard deviation	± 16.354	-	

End points

End points reporting groups

Reporting group title	All patients
Reporting group description: All patients with HO included in the study.	
Subject analysis set title	Patients aged ≥ 6 to <18 years
Subject analysis set type	Full analysis
Subject analysis set description: Patients aged ≥ 6 to <18 years	
Subject analysis set title	Patients aged ≥ 18 years
Subject analysis set type	Full analysis
Subject analysis set description: Patients aged ≥ 18 years	
Subject analysis set title	Patients aged <12 years
Subject analysis set type	Full analysis
Subject analysis set description: Patients aged <12 years	
Subject analysis set title	Patients aged ≥ 12 years
Subject analysis set type	Full analysis
Subject analysis set description: Patients aged ≥ 12 years	

Primary: Patients with $\geq 5\%$ BMI reduction from baseline

End point title	Patients with $\geq 5\%$ BMI reduction from baseline ^[1]
End point description: The proportion of patients with HO who achieved at least 5% reduction from baseline in BMI after 16 weeks of treatment with setmelanotide. The summary of the primary endpoint and the associated 2-sided 90% Clopper-Pearson confidence interval is provided. A p-value of <0.0001 was calculated from a one-sided exact binomial test comparing to the null hypothesis proportion of 0.05 (which comes from a historical control rate of 5%).	
End point type	Primary
End point timeframe: From baseline to Week 16.	
Notes:	

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis of the primary endpoint was planned or performed because this was an open-label study with no comparator group. A comparison with a historical control group is described above.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percent				
number (confidence interval 90%)	88.9 (69.0 to 98.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Composite reduction in BMI Z-score and change in body weight

End point title	Composite reduction in BMI Z-score and change in body weight
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End point description:

Composite proportion of patients aged ≥ 6 to < 18 years with ≥ 0.2 reduction of BMI Z-score and patients aged ≥ 18 years with $\geq 5\%$ reduction of body weight from baseline after 16 weeks of setmelanotide. The summary of the endpoint and the associated 2-sided 90% Clopper-Pearson confidence interval is provided.

A p-value of < 0.0001 was calculated from a one-sided exact binomial test comparing to the null hypothesis proportion of 0.05 (which comes from a historical control rate of 5%).

End point type	Secondary
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End point timeframe:

From baseline to Week 16.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percent				
number (confidence interval 90%)	88.9 (69.0 to 98.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in BMI Z-score in patients aged ≥ 6 to < 18 years

End point title	Reduction in BMI Z-score in patients aged ≥ 6 to < 18 years
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End point description:

The proportion of patients aged ≥ 6 to < 18 years with HO with ≥ 0.2 reduction of BMI Z-score from baseline at 16 weeks of treatment with setmelanotide. The summary of the endpoint and the associated 2-sided 90% Clopper-Pearson confidence interval is provided.

A p-value of < 0.0001 was calculated from a one-sided exact binomial test comparing to the null hypothesis proportion of 0.05 (which comes from a historical control rate of 5%).

End point type	Secondary
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End point timeframe:

From baseline to Week 16.

End point values	Patients aged ≥6 to <18 years			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: percent				
number (confidence interval 90%)	92.3 (68.4 to 99.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in body weight in patients aged ≥18 years

End point title	Reduction in body weight in patients aged ≥18 years
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End point description:

The proportion of patients aged ≥18 years with HO with ≥5% reduction of body weight from baseline at 16 weeks of treatment with setmelanotide. The summary of the endpoint and the associated 2-sided 90% Clopper-Pearson confidence interval is provided.

A p-value of <0.0001 was calculated from a one-sided exact binomial test comparing to the null hypothesis proportion of 0.05 (which comes from a historical control rate of 5%).

End point type	Secondary
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End point timeframe:

From baseline to Week 16.

End point values	Patients aged ≥18 years			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: percent				
number (confidence interval 90%)	80.0 (34.3 to 99.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in waist circumference - ≥18 years of age

End point title	Change in waist circumference - ≥18 years of age
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End point description:

The change in waist circumference from baseline in patients aged ≥18 years at 16 weeks of treatment with setmelanotide. The summary of the primary endpoint and the associated 2-sided 90% Clopper-Pearson confidence interval is provided.

End point type	Secondary
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End point timeframe:

From baseline to Week 16.

End point values	Patients aged ≥18 years			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: percent				
arithmetic mean (confidence interval 90%)	-8.13 (-11.832 to -4.419)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in waist circumference - <18 years of age

End point title	Change in waist circumference - <18 years of age
End point description: The change in waist circumference from baseline in patients aged <18 years at 16 weeks of treatment with setmelanotide. The summary of the primary endpoint and the associated 2-sided 90% Clopper-Pearson confidence interval is provided.	
End point type	Secondary
End point timeframe: From baseline to Week 16.	

End point values	Patients aged ≥6 to <18 years			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: percent				
arithmetic mean (confidence interval 90%)	-11.14 (-14.050 to -8.233)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in hunger score - <12 years of age

End point title	Change in hunger score - <12 years of age
End point description: The change in daily hunger score from baseline in patients aged <12 years at 16 weeks of treatment with setmelanotide. The summary of the primary endpoint and the associated 2-sided 90% Clopper-Pearson confidence interval is provided.	
End point type	Secondary

End point timeframe:

From baseline to Week 16.

End point values	Patients aged <12 years			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: percent				
arithmetic mean (confidence interval 90%)	-62.02 (-84.741 to -39.307)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in hunger score - ≥12 years of age

End point title	Change in hunger score - ≥12 years of age
End point description: The change in daily hunger score from baseline in patients aged ≥12 years at 16 weeks of treatment with setmelanotide. The summary of the primary endpoint and the associated 2-sided 90% Clopper-Pearson confidence interval is provided.	
End point type	Secondary
End point timeframe: From baseline to Week 16.	

End point values	Patients aged ≥12 years			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: percent				
arithmetic mean (confidence interval 90%)	-65.26 (-84.512 to -46.017)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to Week 16 of treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	All patients
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Reporting group description:

All patients with HO included in the study.

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 18 (5.56%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 18 (100.00%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	4		
Injection site pain			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
Injection site pruritus			

subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Injection site erythema			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Injection site induration			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Injection site swelling			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Erection increased			
subjects affected / exposed ^[1]	3 / 11 (27.27%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Psychiatric disorders			
Conversion disorder			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Investigations			

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Blood uric acid increased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Hepatic enzyme increased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2		
Weight decreased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2		
Radius fracture subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Congenital, familial and genetic disorders Type V hyperlipidaemia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2		
Balance disorder subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Seizure			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Speech disorder</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 18 (5.56%)</p> <p>1</p> <p>1 / 18 (5.56%)</p> <p>1</p>		
<p>Blood and lymphatic system disorders</p> <p>Anaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 18 (5.56%)</p> <p>1</p>		
<p>Gastrointestinal disorders</p> <p>Nausea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain upper</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Gastritis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Portal hypertensive gastropathy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>11 / 18 (61.11%)</p> <p>15</p> <p>6 / 18 (33.33%)</p> <p>8</p> <p>4 / 18 (22.22%)</p> <p>4</p> <p>3 / 18 (16.67%)</p> <p>3</p> <p>1 / 18 (5.56%)</p> <p>2</p> <p>1 / 18 (5.56%)</p> <p>1</p> <p>1 / 18 (5.56%)</p> <p>1</p>		
<p>Hepatobiliary disorders</p> <p>Hypertransaminasaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hepatic steatosis</p>	<p>2 / 18 (11.11%)</p> <p>2</p>		

subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation			
subjects affected / exposed	6 / 18 (33.33%)		
occurrences (all)	6		
Acne			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Rash erythematous			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Scoliosis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Infections and infestations			
COVID-19			
subjects affected / exposed	4 / 18 (22.22%)		
occurrences (all)	5		
Upper respiratory tract infection			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Administration site cellulitis			

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Staphylococcal abscess			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: This denominator includes only the male subjects in the group (N = 11).

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 September 2021	There was one protocol amendment. In this amendment, in addition to some clarifications or minor changes to inclusion and exclusion criteria, and administrative updates, the patient population was revised to allow older patients to be included (due to the rare nature of the disease under investigation) and the number of patients aged 6-10 years was restricted to a maximum of 10. Additionally, the primary endpoint was changed from an evaluation of weight loss to a reduction in BMI. Also, secondary endpoints were revised to define key secondary endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported