Clinical trial results:
An Open Label, 1-Year Trial, including a Double-Blind Placebo-Controlled Withdrawal Period, of Setmelanotide (RM-493), a Melanocortin 4 Receptor (MC4R) Agonist, in Early Onset POMC Deficiency Obesity due to Bi-Allelic Loss-of-Function POMC or PCSK1 Genetic Mutation

Summary

EudraCT number	2016-002320-83
Trial protocol	DE GB FR BE ES
Global end of trial date	16 July 2020

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	RM-493-012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02896192
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rhythm Pharmaceuticals, Inc.
Sponsor organisation address	222 Berkeley Street, Boston, United States, MA 02116
Public contact	Chief Medical Officer, Rhythm Pharmaceuticals, Inc., +1 857-264-4280, EU_medinfo@rhythmtx.com
Scientific contact	Chief Medical Officer, Rhythm Pharmaceuticals, Inc., +1 857-264-4280, EU_medinfo@rhythmtx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002209-PIP01-17
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	24 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 May 2020
Global end of trial reached?	Yes
Global end of trial date	16 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate statistically significant and clinically meaningful effects of setmelanotide on percent body weight change in patients with pro-opiomelanocortin (POMC) deficiency obesity due to rare bi-allelic or loss-of function mutations at the end of 1 year of treatment.

Protection of trial subjects:

The IRB/IEC 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. The protocol, investigator brochure (IB), informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents was provided to the IRB/IEC by the Investigator.

Although the study procedures and assessments required per protocol were classified as "No or Minimal Risk" (apart from DEXA which is classified as "Minor Increase over Minimal Risk") per the 2008 Guidance Document "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Pediatric Population", considerations for reducing pain in distress in participants younger than 18 years of age were included in the protocol.

Background therapy:

Unless concomitant medications were likely to present a strong potential safety concern, to allow as many as possible patients with this ultra-rare condition to participate in the study, patients were allowed chronic concomitant medications while participating in the study, including:
1) Growth hormone
2) Contraceptives
3) Hormone replacement therapy (female patients were permitted hormonal contraception as well as hormone replacement therapy)
4) Anti-hypertensives
5) Statins and other lipid-lowering therapies
6) Thyroxine or other thyroid supplements
7) Other medications commonly used in patients with obesity: endocrine therapies (e.g., estrogens, Fosamax, hydrocortisone, vitamin and calcium supplements, diabetic therapies including insulin); and other medications (e.g., carnitor, Coenzyme Q10, vitamins, anti-constipation medications, anti-allergic medications).
8) Except for low threshold drugs (i.e., anticonvulsants, digoxin, Coumadin, etc.), other medications were permitted if the patient was on a stable dose upon consultation with the Sponsor.

Medications that could impact the efficacy assessments during the study were prohibited.
Anorectic agents or drugs with anorexia as a non-rare side effect were prohibited for the duration of the study.

Evidence for comparator:

No active comparator was used in the study, but the study was powered based upon natural history data. There was a double-blind randomized withdrawal period, which included 4 weeks placebo and 4 weeks active treatment.

Actual start date of recruitment	14 February 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	15
EEA total number of subjects	13

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

Subject disposition

Recruitment

Recruitment details:

Patients aged >= 6 years, with bi-allelic, homozygous / compound heterozygous genetic status for POMC or PCSK1, with loss-of-function (LOF) variant for each allele conferring severe obesity phenotype were eligible. If age ≥18 years, body mass index (BMI) ≥30 kg/m2; if <18 years, BMI ≥95th percentile for age (by gender) on growth chart assessment.

Pre-assignment

Screening details:

At screening, a blood sample was obtained for genotyping for mechanisms considered to be possibly related to the safety or efficacy response to the study medication (e.g., other obesity related genes). Complete physical, relevant bloodwork and other standard assessments were performed. All bloodwork was collected between Study Day -28 and -14.

Period 1

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

Blinding implementation details:

This was an open-label study with a dose titration period lasting 2 to 12 weeks (dependent upon number of dose escalations required to determine an individual’s therapeutic dose) followed by a further 10 weeks of open-label treatment at the therapeutic dose. This was followed by an 8-week withdrawal period (4 weeks placebo and 4 weeks on setmelanotide; timing of each was randomly assigned) then continued treatment with setmelanotide to the end of 1-year's treatment.

Arms

Arm title	All treated patients

Arm description:

All patients treated with setmelanotide, includes a combination of 10 patients enrolled in a 'pivotal cohort' and 5 patients in a 'supplemental' cohort. In total, 13 patients had POMC genetic mutations, and 2 patients had PCSK1 genetic mutations.

Arm type	Experimental
Investigational medicinal product name	Setmelanotide
Investigational medicinal product code	RM-493-mPEG-DSPE
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Study patients were administered study drug by subcutaneous (SC) injection once daily (in the morning). The dose titration phase lasted up to 12 weeks with assessments every 2 weeks to determine if a dose should be increased. Once the patient’s therapeutic dose was reached, the same dose was administered for up to 1 year (except during a planned 4-week withdrawal period after a minimum of 12 weeks treatment at the therapeutic dose). Initial doses administered were 1.0 mg (adult patients) or 0.5 mg (paediatric and adolescent patients), and the maximum potential dose following the dose titration process was 3.0 mg or 2.5 mg daily depending on the maximum approved dose in the specific participating country as well as the age of the patient.

Number of subjects in period 1	All treated patients
Started	15
Completed	12
Not completed	3
Lost to follow-up	1
Lack of efficacy	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	All treated patients

Reporting group description:

All patients treated with setmelanotide, includes a combination of 10 patients enrolled in a 'pivotal cohort' and 5 patients in a 'supplemental' cohort. In total, 13 patients had POMC genetic mutations, and 2 patients had PCSK1 genetic mutations.

Reporting group values	All treated patients	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
Children (2-11 years)	5	5	
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	5	5	
Age continuous Units: years			
arithmetic mean	17.20		
standard deviation	± 7.02	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	9	9	
Genetic mutation			
Patients with POMC or PCSK1 mutations were eligible to participate.			
Units: Subjects			
POMC	13	13	
PCKS1	2	2	
Body mass index Units: kg/m2			
arithmetic mean	39.17		
standard deviation	± 8.21	-	
Weight Units: kg			
arithmetic mean	111.26		
standard deviation	± 35.81	-	
Waist circumference Units: cm			
arithmetic mean	118.09		
standard deviation	± 18.62	-	

End points

End points reporting groups

Reporting group title	All treated patients

Reporting group description:

All patients treated with setmelanotide, includes a combination of 10 patients enrolled in a 'pivotal cohort' and 5 patients in a 'supplemental' cohort. In total, 13 patients had POMC genetic mutations, and 2 patients had PCSK1 genetic mutations.

Primary: Body weight change

End point title	Body weight change[1]

End point description:

The primary endpoint in this study was defined as the proportion of patients who met the ≥10% weight loss threshold (responders) after approximately 1 year of treatment with setmelanotide, compared to the proportion from historical data (at most, 5% responders in the null population). This endpoint analysis was performed solely on designated responders and therefore on the FAS population.

The proportion of patients who had at least 10% weight reduction at ~1 year vs baseline was analysed via the exact binomial test, at 1-sided 5% of significance level, against the null hypothesis that the proportion was less than or equal to 5% and the alternative hypothesis was that the proportion was greater than 5%. The 2-sided 90% CI of the proportion was calculated using the exact Clopper-Pearson method.

Results of the analysis: point estimate: 85.7% (90% CI 61.46, 97.40), p<0.0001, indicating the primary efficacy endpoint was met.

End point type	Primary

End point timeframe:

Baseline to 1 year

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: In this non-comparator study, statistical analysis was based upon comparison with historical data. Details are included with the endpoint description since it is not possible to otherwise enter the analyses without a comparator group.

End point values	All treated patients			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Subjects				
Subjects with at least 10% weight loss	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in body weight

End point title	Percentage change in body weight

End point description:

Mean percentage of body weight change (kg) from baseline after 1 year of treatment with setmelanotide within the DUS population (defined as all patients who received any study drug, demonstrated ≥5 kg weight loss or 5% of body weight over 12-week open-label treatment period, and proceeded into the

double-blind, placebo-controlled withdrawal period).

A linear mixed model repeated measures analysis of variance with a fixed term for time and baseline and a random effect for patients was used. An unstructured covariance matrix was used to model the expected different variances among the participants. In the event the mixed model did not converge with an unstructured covariance matrix, a compound-symmetric then Toeplitz covariance matrix was employed instead.

Results of the analysis: LS mean change: -25.73% (90% CI -28.49, -22.98), p<0.0001, indicating this key secondary efficacy endpoint was met.

End point type	Secondary

End point timeframe:

Change from baseline to Week 52

End point values	All treated patients			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: kg				
arithmetic mean (standard deviation)	-25.83 (± 9.721)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in hunger score

End point title	Change in hunger score

End point description:

Evaluation of the mean percent change in hunger scores (weekly average hunger score of the daily worst [most] hunger score in 24 hours) in patients ≥12 years of age at the end of approximately 1 year of treatment within a single group of patients.

A linear mixed model repeated measures analysis of variance with a fixed term for time and baseline and a random effect for patients was used. An unstructured covariance matrix was used to model the expected different variances among the participants. In the event the mixed model did not converge with an unstructured covariance matrix, a compound-symmetric then Toeplitz covariance matrix was employed instead.

Results of analysis: LS mean change: -27.77% (90% CI -40.58, -14.96), p=0.0005, indicating this key secondary efficacy endpoint was met.

End point type	Secondary

End point timeframe:

From baseline to Week 52

End point values	All treated patients			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percent				
arithmetic mean (standard deviation)	-27.1 (± 28.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Improvement in daily hunger score

End point title	Improvement in daily hunger score

End point description:

Evaluation of the proportion of patients ≥12 years of age achieving at least 25% improvement in worst (most) hunger score following 1 year of treatment with setmelanotide. This endpoint analysis was performed solely on designated responders and therefore based on the FAS population.

The proportion of patients who had at least 25% improvement in hunger score at ~1 year vs baseline was analysed via the exact binomial test, at 1-sided 5% of significance level, against the null hypothesis that the proportion was less than or equal to 5% and the alternative hypothesis was that the proportion was greater than 5%. The 2-sided 90% CI of the proportion was calculated using the exact Clopper-Pearson method.
Results of the analysis: point estimate: 50% (90% CI: 19.29, 80.71); p=0.0004, indicating this key secondary efficacy endpoint was met.

End point type	Secondary

End point timeframe:

From baseline to Week 52.

End point values	All treated patients			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Subjects				
Subjects with at least 25% improvement	4			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline to end of treament	
Adverse event reporting additional description:	
The relatedness assessment was as reported by the investigator.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	All treated patients
Reporting group description:	
All patients treated with setmelanotide, includes a combination of 10 patients enrolled in a 'pivotal cohort' and 5 patients in a 'supplemental' cohort. In total, 13 patients had POMC genetic mutations, and 2 patients had PCSK1 genetic mutations.	

Serious adverse events	All treated patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 15 (40.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Pleurisy			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Panic attack			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 15 (6.67%)		
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 treated patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	7		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Injection site erythema			

subjects affected / exposed	12 / 15 (80.00%)			
occurrences (all)	59			
Injection site oedema				
subjects affected / exposed	9 / 15 (60.00%)			
occurrences (all)	29			
Injection site pruritus				
subjects affected / exposed	9 / 15 (60.00%)			
occurrences (all)	20			
Fatigue				
subjects affected / exposed	6 / 15 (40.00%)			
occurrences (all)	7			
Chills				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	4			
Injection site pain				
subjects affected / exposed	4 / 15 (26.67%)			
occurrences (all)	4			
Asthenia				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	3			
Injection site bruising				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	3			
Pyrexia				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	3			
Injection site induration				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	2			
Hyperthermia				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Injection site discolouration				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Injection site nodule				

subjects affected / exposed occurrences (all) Temperature intolerance subjects affected / exposed occurrences (all) Thirst subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Immune system disorders Multiple allergies subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1		
Reproductive system and breast disorders Spontaneous penile erection subjects affected / exposed occurrences (all) Dysmenorrhoea subjects affected / exposed occurrences (all) Erection increased subjects affected / exposed occurrences (all)	 2 / 15 (13.33%) 5 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all) Sneezing subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Psychiatric disorders Suicidal ideation subjects affected / exposed occurrences (all)	 2 / 15 (13.33%) 3		

Depressed mood subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		
Restlessness subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		
Sleep disorder subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		
Depression subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Irritability subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Nightmare subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Investigations			
Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Blood potassium decreased subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Blood uric acid increased subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
International normalised ratio increased subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Injury, poisoning and procedural complications			

Accidental overdose			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ligament sprain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin laceration			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Sinus bradycardia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 15 (53.33%)		
occurrences (all)	14		
Disturbance in attention			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Parosmia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Sciatica			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood and lymphatic system disorders			

Iron deficiency anaemia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 5		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	8 / 15 (53.33%) 18		
Vomiting subjects affected / exposed occurrences (all)	8 / 15 (53.33%) 17		
Abdominal pain subjects affected / exposed occurrences (all)	4 / 15 (26.67%) 10		
Diarrhoea subjects affected / exposed occurrences (all)	5 / 15 (33.33%) 7		
Dry mouth subjects affected / exposed occurrences (all)	4 / 15 (26.67%) 5		
Lip dry subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Constipation subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Gastritis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation			
subjects affected / exposed	15 / 15 (100.00%)		
occurrences (all)	24		
Alopecia			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Dry skin			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	4		
Rash papular			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Hidradenitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Perioral dermatitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rash erythematous			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin hypopigmentation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal and urinary disorders			
Leukocyturia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Proteinuria			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Endocrine disorders			
Cortisol deficiency			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	8		
Arthralgia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Muscle contracture			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Muscular weakness			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	7 / 15 (46.67%)		
occurrences (all)	16		
Gastroenteritis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pharyngitis streptococcal			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypovitaminosis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Selenium deficiency			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vitamin A deficiency			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 August 2016	Ths amendment included the following changes: Revised definition of females of nonchildbearing potential in inclusion criterion 5, and revised inclusion criterion 6 related to male participants of childbearing potential requiring double barrier contraception.
01 September 2016	Ths amendment included the following changes for Germany: Revised highest allowable dose titration to 2.5 mg rather than 3.0 mg, and clarified dose titration; updated inclusion 4; added exclusion 15 regarding institutionalized patients or dependents of the sponsor, Investigator or study site were ineligible for the study; and added Appendix to protocol documenting considerations specific to pediatric populations.
14 September 2016	Ths amendment included the following changes for France: Added the same 2008 Guidance for Reducing Pain and Suffering in adolescent populations; clarified inclusion and exclusions, contraception requirements were brought into alignment with GCP/ICH Guidelines, and end of trial definition and clarification of Termination/Final Visit assessments.
23 February 2017	This amendment incorporated revisions from the previous two country amendments in a global update and additionally, two Global Hunger Questions were added to the study to help assess hunger and were to be administered at clinic visits as specified within the protocol. Other substantial updates included: Modified the rationale for doses selected to have the protocol encompass all competent regional authorities' requests. Modified exclusion criterion 6 to have globally acceptable language with regard to restrictive or obstructive lung disease referencing NYHA Class 3 heart failure, etc. Modified dose titration maximum allowable dose language (and duration of dose titration) to encompass all competent authorities' request. 2008 Guidance for Reducing The Pain and Suffering in the adolescent population was incorporated.
22 May 2017	This amendment allowed inclusion of pediatric patients as young as 6 years of age; included bone age assessments; included neurocognitive assessments in patients 6 to 16 years of age; included dose titration guidelines for patients between 6 to 11 years of age; and included age appropriate hunger questions, quality of life assessments, and pediatric age range versions of C-SRS and PHQ-9.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/3313729