Clinical trial results:
A phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate efficacy and safety of octreotide capsules in patients who previously tolerated and demonstrated biochemical control on injectable somatostatin receptor ligands (SRL) treatment

Summary

EudraCT number	2017-000737-31
Trial protocol	GB DE HU NL SE DK PL IT BG LV SI RO
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	11 September 2020
First version publication date	11 September 2020

Trial information

Trial identification

Sponsor protocol code	OOC-ACM-303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03252353
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chiasma, Inc.
Sponsor organisation address	140 Kendrick Street, Building C East, Needham, United States, MA 02494
Public contact	Asi Haviv, Chiasma, Inc., +972 8-939-3888, Asi@chiasmapharma.com
Scientific contact	Asi Haviv, Chiasma, Inc., +972 8-939-3888, Asi@chiasmapharma.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	Interim
Date of interim/final analysis	11 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 June 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To assess maintenance of biochemical control with octreotide capsules compared to placebo in patients with acromegaly, who previously demonstrated biochemical control on somatostatin receptor ligands (SRLs)

Protection of trial subjects:

Not applicable

Background therapy:

Parenteral SRL monotherapy (octreotide or lanreotide but not pasireotide).

Evidence for comparator:

Not applicable

Actual start date of recruitment	30 August 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Turkey: 3
Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Slovenia: 2
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Latvia: 1

Worldwide total number of subjects	56
EEA total number of subjects	22

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)	43
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was performed from 30 Aug 2017 (first site intiated) to 13 Jun 2019 (last patient completed core study period).

Pre-assignment

Screening details:

The Screening period consisted of 2 screening visits to assess whether the average insulin-like growth factor-1 (IGF-1) level was ≤ 1 times the upper limit of normal (ULN) to determine eligibility. Screening visit 2 was scheduled within 2 weeks prior to randomisation.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Octreotide

Arm description:

Octreotide 40, 60, or 80 mg/day (individual dose titration).

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

Dosage and administration details:

Octreotide treatment was started at a total dose of 40 mg/day. Dose escalation (based on measurement of the patient's circulating IGF-1 levels and acromegaly-related Symptoms) was performed in a stepwise manner to 60 mg/day or 80 mg/day. Study drug was taken twice daily, in the morning and in the evening.

Arm title	Placebo

Arm description:

Octreotide matching placebo

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

Dosage and administration details:

Octreotide-matching placebo was started at a capsule number matching a total dose of 40 mg/day. Dose escalation (based on measurement of the patient's circulating IGF-1 levels and acromegaly-related Symptoms) was performed in a stepwise manner to a capsule number matching 60 mg/day or 80 mg/day. Study drug was taken twice daily, in the morning and in the evening.

Number of subjects in period 1	Octreotide	Placebo
Started	28	28
Completed	28	28

Baseline characteristics

Reporting groups	
Reporting group title	Octreotide
Reporting group description:	
Octreotide 40, 60, or 80 mg/day (individual dose titration).	
Reporting group title	Placebo
Reporting group description:	
Octreotide matching placebo	

Reporting group values	Octreotide	Placebo	Total
Number of subjects	28	28	56
Age categorical			
Only adult subjects were enrolled.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	21	22	43
From 65-84 years	7	6	13
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	55.3	54.2	
standard deviation	± 11.97	± 10.96	-
Gender categorical			
Units: Subjects			
Female	12	14	26
Male	16	14	30

Subject analysis sets	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
This population includes all randomized patients. The FAS served as the primary efficacy analysis population for the DPC period of the study. The safety set and the per protocol set were identical to the FAS.	

Reporting group values	Full analysis set		
Number of subjects	56		
Age categorical			
Only adult subjects were enrolled.			
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)	43		
From 65-84 years	13		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	54.7		
standard deviation	± 11.38		
Gender categorical			
Units: Subjects			
Female	26		
Male	30		

End points

End points reporting groups

Reporting group title	Octreotide
Reporting group description:	
Octreotide 40, 60, or 80 mg/day (individual dose titration).	
Reporting group title	Placebo
Reporting group description:	
Octreotide matching placebo	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
This population includes all randomized patients. The FAS served as the primary efficacy analysis population for the DPC period of the study. The safety set and the per protocol set were identical to the FAS.	

Primary: Proportion of Patients Who Maintain Their Biochemical Response at the End of the Double Blind Placebo Controlled Period

End point title	Proportion of Patients Who Maintain Their Biochemical Response at the End of the Double Blind Placebo Controlled Period
End point description:	
Maintenance of response was defined by using the average IGF-1 level of the last 2 available assessments between weeks 34 and 36 in the DPC period. If the average IGF-1 is ≤ 1×ULN, a patient was classified as a responder (i.e., maintained their biochemical response). If the average IGF-1 is > 1×ULN, a patient was classified as a non-responder. Patients who discontinued study medication during the DPC period for any reason were classified as non-responders for the primary analysis, regardless of their IGF-1 values.	
End point type	Primary
End point timeframe:	
Week 36	

End point values	Octreotide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: Subjects				
Responder	16	5		
Non-responder	12	23		

Statistical analyses

Statistical analysis title	Analysis of primary endpoint
Statistical analysis description:	
An exact logistic regression model, with covariates for treatment, baseline SRL dose (low vs mid or high) and baseline IGF-1 level (< median vs ≥ median) was used.	
Comparison groups	Octreotide v Placebo

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0079
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.7674
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.444
upper limit	28.2115

Notes:

[1] - If the two-sided p-value was < 0.05, octreotide capsules were declared superior to placebo.

Secondary: Proportion of Patients Who Maintain GH Response at the End of the Double Blind Placebo Controlled Period

End point title	Proportion of Patients Who Maintain GH Response at the End of the Double Blind Placebo Controlled Period

End point description:

Maintenance of GH response was defined as having mean Growth Hormone (5 measurements 30 minutes apart) < 2.5 ng/mL at the end of the double blind placebo controlled period, out of those who were responders on SRL injections at Screening.

End point type	Secondary

End point timeframe:

Week 36

End point values	Octreotide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: Subjects				
Responder	21	7		
Non-responder	7	21		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Patients Who Begin Rescue Treatment

End point title	Proportion of Patients Who Begin Rescue Treatment

End point description:

Proportion of Patients who Began Rescue Treatment Prior to and Including Week 36.

End point type	Secondary

End point timeframe:

Week 36

End point values	Octreotide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: Subjects	7	19		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
1 year, 10 months	
Adverse event reporting additional description:	
Safety population: All participants enrolled in the study who received any amount of the study drug.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Octreotide
Reporting group description:	
Octreotide treatment was started at a total dose of 40 mg/day. Dose escalation was based on measurement of the patient's circulating IGF-1 levels and acromegaly-related symptoms. Dose escalation was performed in a stepwise manner to 60 mg/day or 80 mg/day.	
Reporting group title	Placebo
Reporting group description:	
Octreotide matching placebo	

Serious adverse events	Octreotide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 28 (7.14%)	1 / 28 (3.57%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Joint dislocation			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Arthritis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Octreotide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 28 (100.00%)	27 / 28 (96.43%)	
Investigations			
Blood glucose increased			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 28 (10.71%)	1 / 28 (3.57%)	
occurrences (all)	5	2	
Gamma-glutamyltransferase increased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 28 (3.57%)	3 / 28 (10.71%)	
occurrences (all)	1	4	
Insulin-like growth factor increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 28 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Weight increased			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 28 (7.14%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
Nervous system disorders			
Carpal tunnel syndrome			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 28 (14.29%)	4 / 28 (14.29%)	
occurrences (all)	5	5	
Headache			
alternative assessment type: Systematic			

subjects affected / exposed	4 / 28 (14.29%)	9 / 28 (32.14%)	
occurrences (all)	7	17	
Hypoaesthesia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 28 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Paraesthesia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 28 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 28 (7.14%)	7 / 28 (25.00%)	
occurrences (all)	2	8	
Influenza like illness			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 28 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Oedema peripheral			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 28 (7.14%)	3 / 28 (10.71%)	
occurrences (all)	2	3	
Pain			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 28 (7.14%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Peripheral swelling			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 28 (10.71%)	4 / 28 (14.29%)	
occurrences (all)	4	4	
Gastrointestinal disorders			
Abdominal discomfort			
alternative assessment type: Systematic			

subjects affected / exposed	4 / 28 (14.29%)	3 / 28 (10.71%)	
occurrences (all)	4	4	
Abdominal pain			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 28 (7.14%)	2 / 28 (7.14%)	
occurrences (all)	3	2	
Abdominal pain upper			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 28 (3.57%)	3 / 28 (10.71%)	
occurrences (all)	1	3	
Constipation			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 28 (10.71%)	4 / 28 (14.29%)	
occurrences (all)	4	5	
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 28 (28.57%)	6 / 28 (21.43%)	
occurrences (all)	9	6	
Dyspepsia			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 28 (10.71%)	1 / 28 (3.57%)	
occurrences (all)	3	2	
Flatulence			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Large intestine polyp			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 28 (7.14%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 28 (21.43%)	3 / 28 (10.71%)	
occurrences (all)	7	3	

Tongue disorder			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 28 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 28 (14.29%)	0 / 28 (0.00%)	
occurrences (all)	4	0	
Hepatobiliary disorders			
Cholelithiasis			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 28 (7.14%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 28 (21.43%)	7 / 28 (25.00%)	
occurrences (all)	10	8	
Night sweats			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Psychiatric disorders			
Anxiety			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed	9 / 28 (32.14%)	16 / 28 (57.14%)	
occurrences (all)	11	28	
Arthritis			
alternative assessment type: Systematic			

subjects affected / exposed	2 / 28 (7.14%)	2 / 28 (7.14%)	
occurrences (all)	3	4	
Back pain			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 28 (7.14%)	4 / 28 (14.29%)	
occurrences (all)	2	5	
Musculoskeletal pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	4	
Osteoarthritis			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 28 (10.71%)	0 / 28 (0.00%)	
occurrences (all)	3	0	
Pain in extremity			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 28 (0.00%)	3 / 28 (10.71%)	
occurrences (all)	0	3	
Soft tissue swelling			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 28 (3.57%)	3 / 28 (10.71%)	
occurrences (all)	1	3	
Infections and infestations			
Nasopharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 28 (10.71%)	4 / 28 (14.29%)	
occurrences (all)	33	5	
Sinusitis			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 28 (10.71%)	0 / 28 (0.00%)	
occurrences (all)	3	0	
Upper respiratory tract infection			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 28 (7.14%)	1 / 28 (3.57%)	
occurrences (all)	6	2	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 28 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2017	Changed the order of the secondary objectives and secondary efficacy endpoints; added an exploratory endpoint (ie, proportion of patients who require rescue medication [eg, re-initiate SRL treatment]); and modified the definition of the FAS.
29 November 2017	Updated the Sponsor's street address; removed the following secondary objective: "to assess relative change in IGF-1 and GH on octreotide capsules compared to placebo"; added the following secondary endpoint: "proportion of patients who begin rescue treatment prior to and including week 36"; recategorized 2 of the endpoints from secondary endpoints to descriptive endpoints; removed the following exploratory endpoint: "proportion of patients who require rescue medication (eg, re-initiate SRL treatment)"; modified the statistical methods for the secondary efficacy analyses; and added statistical methods for the descriptive endpoint analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported