Clinical trial results:
A Phase 2b/3 study to evaluate the safety, tolerability, and effects of livoletide (AZP-531), an unacylated ghrelin analog, on food-related behaviors in patients with Prader-Willi syndrome

Summary

EudraCT number	2018-003062-13
Trial protocol	FR GB ES BE NL IT
Global end of trial date	25 May 2020

Results information

Result version number	v1 (current)
This version publication date	06 February 2021
First version publication date	06 February 2021

Trial information

Trial identification

Sponsor protocol code	AZP01-CLI-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03790865
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Millendo Therapeutics
Sponsor organisation address	8 rue Berjon, Lyon, France, 69009
Public contact	Clinical Trial Information, Millendo Therapeutics SAS, +33 4 72 18 94 28, harisseh@millendo.com
Scientific contact	Clinical Trial Information, Millendo Therapeutics SAS, +33 4 72 18 94 28, harisseh@millendo.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 September 2020
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	25 May 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Core Period
Phase 2b
To demonstrate the efficacy of a 3-month treatment with livoletide as compared to placebo for reducing caregiver-observed food-related behavior as assessed by the Hyperphagia Questionnaire for Clinical Trials (HQ-CT).
Note: the results presented here are only from the Phase 2b Core Period part of the study which was completed before the study was terminated.

Phase 3
To demonstrate the efficacy of a 6-month treatment with livoletide as compared to placebo for reducing caregiver-observed food-related behavior as assessed by HQ-CT.
Note: Phase 3 was not started because the clinical trial was terminated early by the Sponsor during the Phase 2b part of the study.

Protection of trial subjects:

The Investigator was responsible for ensuring that patients did not undergo any study-related examination or activity before giving informed consent. The patient must have given written consent after the receipt of detailed information regarding the study. The verbal explanation covered all the elements specified in the written information provided to the patient. If the written informed consent was provided by the legal guardian because the patient was unable to do so, a written or verbal assent from the patient must have also been obtained.

The Investigators have informed the patient of the aims, methods, anticipated benefits, and potential hazards of the study, including any discomfort it may entail. The patient must have been given every opportunity to clarify any points he/she did not understand and must have been provided with more information if requested. At the end of the interview, the patient may have been given time to reflect and could request more time if was needed. The patient and/or legal guardian have been required to sign and date the informed consent form. After completion, informed consent forms were kept and archived by the Investigator in the Investigator study file.

It was to be emphasized to the patient that he or she was at liberty to either discontinue study drug and/or withdraw consent to participate at any time, without penalty or loss of benefits to which he or she was otherwise entitled. Patients who refused to give or withdraw written informed consent may have not been included or continued in this study, but this did not affect their subsequent care.

In addition, a safety data review was performed at a regular basis during the trial by an external Data Monitoring Committee (DMC) operating independently of the Sponsor to make recommendations for the conduct of the study based on safety data. The DMC did operate under the rules of an approved charter defining the roles and responsibilities of its members.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 March 2019
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	Netherlands: 8
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	France: 34
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	United States: 66
Worldwide total number of subjects	158
EEA total number of subjects	82

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)	26
Adolescents (12-17 years)	41
Adults (18-64 years)	91
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Original protocol
For Phase 2b, a total of 50 patients per group will need to be randomized.
Amendment v1.2
For Phase 2b, a total of approximately 50 patients per group (8 to 65 years of age) will need to be randomized. In addition to this cohort of 150 patients, a separate cohort of patients 4 to 7 years of age will also be randomized.

Pre-assignment

Screening details:

Screening Period was up to 4 weeks
After signing informed consent, patients with PWS entered the Screening Period to assess preliminary eligibility for the study based on the inclusion and exclusion criteria. In addition, pertinent information was collected such as past medical history, demographic data, and prior and current medications

Period 1

Period 1 title	Treatment Period: Phase 2b Core Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Low-dose livoletide

Arm description:

Daily subcutaneous injection of livoletide 60 µg/kg

Arm type	Experimental
Investigational medicinal product name	Livoletide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The study drug will be administered subcutaneously as a single injection under a full skin fold of the anterior abdominal region, at rotating sites, every day during the treatment period.

Arm title	High-dose livoletide

Arm description:

Daily subcutaneous injection of livoletide 120 µg/kg

Arm type	Experimental
Investigational medicinal product name	Livoletide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The study drug will be administered subcutaneously as a single injection under a full skin fold of the anterior abdominal region, at rotating sites, every day during the treatment period.

Arm title	Placebo

Arm description:

Daily subcutaneous injection of 0.9% NaCl

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo will be administered subcutaneously as a single injection under a full skin fold of the anterior abdominal region, at rotating sites, every day during the treatment period.

Number of subjects in period 1	Low-dose livoletide	High-dose livoletide	Placebo
Started	52	52	54
Completed	52	52	54

Baseline characteristics

Reporting groups	
Reporting group title	Low-dose livoletide
Reporting group description:	
Daily subcutaneous injection of livoletide 60 µg/kg	
Reporting group title	High-dose livoletide
Reporting group description:	
Daily subcutaneous injection of livoletide 120 µg/kg	
Reporting group title	Placebo
Reporting group description:	
Daily subcutaneous injection of 0.9% NaCl	

Reporting group values	Low-dose livoletide	High-dose livoletide	Placebo
Number of subjects	52	52	54
Age categorical 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)	6	9	10
Adolescents (12-17 years)	16	13	13
Adults (18-64 years)	30	30	31
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	28	28	32
Male	24	24	22
Baseline HQ-CT Units: score on a scale			
arithmetic mean	20.4	19.5	20.5
standard deviation	± 6.37	± 6.34	± 5.87

Reporting group values	Total		
Number of subjects	158		
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)	25		
Adolescents (12-17 years)	42		
Adults (18-64 years)	91		

From 65-84 years	0		
85 years and over	0		

Gender categorical Units: Subjects			
Female	88		
Male	70		
Baseline HQ-CT Units: score on a scale arithmetic mean standard deviation	 -		

Subject analysis sets

Subject analysis set title	Phase 2b Core Period, Eight to 65 years of age
Subject analysis set type	Full analysis

Subject analysis set description:

All analyses were performed for the eight to 65 years of age cohort only. Only one patient < eight years of age was evaluated in the Phase 2b Core Period. This patient was randomized into the placebo group. This patient is not included the analyses.
The Full Analysis Set (FAS) included all randomized patients. Efficacy analyses for the Phase 2b Core Period were performed on the FAS.

Reporting group values	Phase 2b Core Period, Eight to 65 years of age		
Number of subjects	158		
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)	25		
Adolescents (12-17 years)	42		
Adults (18-64 years)	91		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	88		
Male	70		
Baseline HQ-CT Units: score on a scale arithmetic mean standard deviation	 20.2 ± 6.15		

End points

End points reporting groups

Reporting group title	Low-dose livoletide
Reporting group description:	
Daily subcutaneous injection of livoletide 60 µg/kg	
Reporting group title	High-dose livoletide
Reporting group description:	
Daily subcutaneous injection of livoletide 120 µg/kg	
Reporting group title	Placebo
Reporting group description:	
Daily subcutaneous injection of 0.9% NaCl	
Subject analysis set title	Phase 2b Core Period, Eight to 65 years of age
Subject analysis set type	Full analysis
Subject analysis set description:	
All analyses were performed for the eight to 65 years of age cohort only. Only one patient < eight years of age was evaluated in the Phase 2b Core Period. This patient was randomized into the placebo group. This patient is not included the analyses. The Full Analysis Set (FAS) included all randomized patients. Efficacy analyses for the Phase 2b Core Period were performed on the FAS.	

Primary: Change from Baseline to month 3 in HQ-CT total score

End point title	Change from Baseline to month 3 in HQ-CT total score
End point description:	
HQ-CT is a 9-item caregiver-reported measure of behaviors commonly associated with hyperphagia in patients with Prader–Willi Syndrome. The HQ-CT score range is 0 to 36 where the higher score represents more severe abnormal food related behaviors.	
End point type	Primary
End point timeframe:	
Change from baseline to month 3	

End point values	Low-dose livoletide	High-dose livoletide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	52	54	
Units: score on a scale				
arithmetic mean (standard deviation)	-5.1 (± 7.76)	-3.6 (± 6.08)	-3.3 (± 5.77)	

Statistical analyses

Statistical analysis title	Analysis of the Primary Endpoint
Comparison groups	High-dose livoletide v Placebo v Low-dose livoletide

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.025
Method	Mixed models analysis

Secondary: Change from Baseline to Month 3 in Waist Circumference in Patients Eight to 65 Years of Age Defined as Overweight/Obese

End point title	Change from Baseline to Month 3 in Waist Circumference in Patients Eight to 65 Years of Age Defined as Overweight/Obese

End point description:

The waist circumference was measured in fasting condition at the superior border of iliac crest, according to recommendations from the Anthropometry Procedures Manual of the National Health and Nutrition Examination Survey, Revised 2007.
Overweight/obese patients were defined as follows:
o patients ≥18 years of age: BMI ≥27 kg/m2
o patients 4-17 years of age: BMI ≥90th percentile for the same age and sex

End point type	Secondary

End point timeframe:

Change from baseline to month 3

End point values	Low-dose livoletide	High-dose livoletide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	39	40	
Units: cm				
arithmetic mean (standard deviation)	0.92 (± 5.703)	0.11 (± 4.969)	-0.45 (± 3.674)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline to Month 3 in Total Body Fat Mass in Patients Eight to 65 Years of Age Defined as Overweight/Obese

End point title	Percentage Change from Baseline to Month 3 in Total Body Fat Mass in Patients Eight to 65 Years of Age Defined as Overweight/Obese

End point description:

Total body fat mass was assessed using dual energy X-ray absorptiometry (DXA) scan. DXAs were conducted at each local facility using standardized procedures and settings.
Overweight/obese patients were defined as follows:
o patients ≥18 years of age: BMI ≥27 kg/m2
o patients 4-17 years of age: BMI ≥90th percentile for the same age and sex

End point type	Secondary

End point timeframe:

Change from baseline to month 3

End point values	Low-dose livoletide	High-dose livoletide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	39	40	
Units: Percentage change from baseline				
arithmetic mean (standard deviation)	0.33 (± 3.806)	3.48 (± 4.429)	-0.36 (± 4.302)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Month 3 in Body Weight in Patients Eight to 65 Years of Age Defined as Overweight/Obese

End point title	Change from Baseline to Month 3 in Body Weight in Patients Eight to 65 Years of Age Defined as Overweight/Obese

End point description:

Patients were weighed in fasting condition, clothed (underwear, light gown or light clothing), without footwear or heavy jewelry, using a calibrated scale. The same scale should be used throughout the study if possible. The conditions under which patients are weighed should be kept consistent if possible. Overweight/obese patients were defined as follows:
o patients ≥18 years of age: BMI ≥27 kg/m2
o patients 4-17 years of age: BMI ≥90th percentile for the same age and sex

End point type	Secondary

End point timeframe:

Change from baseline to month 3

End point values	Low-dose livoletide	High-dose livoletide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	39	40	
Units: percentage				
arithmetic mean (standard deviation)	1.39 (± 3.313)	1.79 (± 2.079)	1.06 (± 2.589)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The analysis of Treatment-emergent adverse events (TEAEs) was done starting first dose of study drug and through 30 days after the end of the treatment period

Adverse event reporting additional description:

AEs were experienced by 34 (65.4%) patients in the livoletide 60 µg/mL group, 35 (67.3%) patients in the livoletide 120 µg/mL group, and 37 (68.5%) patients in the placebo group. TEAEs were experienced by 34 (65.4%) patients in the livoletide 60 µg/mL, 34 (65.4%) patients in the livoletide 120 µg/mL, and 34 (63.0%) patients in placebo group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Low-dose livoletide
Reporting group description: -	
Reporting group title	High-dose livoletide
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Low-dose livoletide	High-dose livoletide	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 52 (3.85%)	1 / 52 (1.92%)	1 / 54 (1.85%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Impulse-control disorder			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lower respiratory tract infection			

subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Low-dose livoletide	High-dose livoletide	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 52 (61.54%)	35 / 52 (67.31%)	37 / 54 (68.52%)
Investigations			
Blood pressure systolic increased			
subjects affected / exposed	2 / 52 (3.85%)	0 / 52 (0.00%)	0 / 54 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	1 / 52 (1.92%)	2 / 52 (3.85%)	0 / 54 (0.00%)
occurrences (all)	1	2	0
Contusion			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	2 / 54 (3.70%)
occurrences (all)	0	0	2
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 52 (5.77%)	2 / 52 (3.85%)	3 / 54 (5.56%)
occurrences (all)	6	2	3
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	8 / 52 (15.38%)	6 / 52 (11.54%)	2 / 54 (3.70%)
occurrences (all)	11	6	2
Injection site erythema			
subjects affected / exposed	5 / 52 (9.62%)	2 / 52 (3.85%)	0 / 54 (0.00%)
occurrences (all)	5	2	0
Injection site bruising			
subjects affected / exposed	3 / 52 (5.77%)	5 / 52 (9.62%)	3 / 54 (5.56%)
occurrences (all)	3	5	3
Pyrexia			

subjects affected / exposed	4 / 52 (7.69%)	2 / 52 (3.85%)	1 / 54 (1.85%)
occurrences (all)	4	2	2
Fatigue			
subjects affected / exposed	1 / 52 (1.92%)	2 / 52 (3.85%)	1 / 54 (1.85%)
occurrences (all)	1	2	1
Injection site haematoma			
subjects affected / exposed	3 / 52 (5.77%)	1 / 52 (1.92%)	0 / 54 (0.00%)
occurrences (all)	6	1	0
Injection site mass			
subjects affected / exposed	2 / 52 (3.85%)	1 / 52 (1.92%)	1 / 54 (1.85%)
occurrences (all)	2	1	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 52 (15.38%)	4 / 52 (7.69%)	5 / 54 (9.26%)
occurrences (all)	10	4	5
Abdominal pain			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	2 / 54 (3.70%)
occurrences (all)	2	0	3
Constipation			
subjects affected / exposed	2 / 52 (3.85%)	0 / 52 (0.00%)	1 / 54 (1.85%)
occurrences (all)	2	0	1
Nausea			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	2 / 54 (3.70%)
occurrences (all)	1	0	2
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	4 / 52 (7.69%)	2 / 52 (3.85%)	0 / 54 (0.00%)
occurrences (all)	4	2	0
Psychiatric disorders			
Dermatillomania			
subjects affected / exposed	0 / 52 (0.00%)	2 / 52 (3.85%)	0 / 54 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	2 / 54 (3.70%)
occurrences (all)	1	0	2

Myalgia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	2 / 54 (3.70%)
occurrences (all)	0	0	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 52 (3.85%)	2 / 52 (3.85%)	6 / 54 (11.11%)
occurrences (all)	2	2	6
Influenza			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	4 / 54 (7.41%)
occurrences (all)	0	1	4
Gastroenteritis			
subjects affected / exposed	1 / 52 (1.92%)	2 / 52 (3.85%)	1 / 54 (1.85%)
occurrences (all)	1	2	1
upper respiratory infection			
subjects affected / exposed	0 / 52 (0.00%)	2 / 52 (3.85%)	1 / 54 (1.85%)
occurrences (all)	0	2	2
Ear infection			
subjects affected / exposed	2 / 52 (3.85%)	0 / 52 (0.00%)	0 / 54 (0.00%)
occurrences (all)	2	0	0
Paronychia			
subjects affected / exposed	2 / 52 (3.85%)	0 / 52 (0.00%)	0 / 54 (0.00%)
occurrences (all)	3	0	0
Sinusitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	2 / 54 (3.70%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 November 2018	In this global amendment v1.1: - Pharmacokinetic assessment were added to the Core Period of Phase 2b following United States FDA recommendation. - Clarification of the screening period duration was provided
31 July 2019	In this Global amendment: The protocol was modified to incorporate the inclusion of patients 4 to 7 years of age. Eligibility criteria were updated according to this age range The protocol was modified to clarify the following items: - inclusion criteria number 1, 5, 11, 13 and 14 - dose changes for concomitant medications - description of Women of Child Bearing Potential The protocol was modified to include updates of the non-clinical and the statistical sections

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 April 2020	Top-line data from the double-blind, placebo-controlled part of the ZEPHYR phase 2b study were obtained on 06 Apr 2020, and the study did not meet the primary endpoint or any of the secondary endpoints. Therefore, the phase 2b/3 study as well as livoletide development program were terminated for lack of efficacy.	-

Notes:

Limitations and caveats

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

The double-blind, placebo-controlled phase 2b study did not meet the primary endpoint or any of the secondary endpoints. Therefore, the Sponsor has decided to discontinue further development of livoletide.

Notes: