Clinical trial results:
A Phase III, Randomized, Double-Blind, Placebo-Controlled, Efficacy, and Safety Study of Balovaptan in Adults With Autism Spectrum Disorder With a 2-Year Open-Label Extension

Summary

EudraCT number	2017-004378-32
Trial protocol	GB ES FR IT
Global end of trial date	06 July 2020

Results information

Result version number	v1 (current)
This version publication date	07 March 2021
First version publication date	07 March 2021

Trial information

Trial identification

Sponsor protocol code	WN39434

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03504917
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann- La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global-roche-genentech-trials@gene.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	03 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 July 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study will evaluate the efficacy, safety, and pharmacokinetics of 10 mg of oral administration balovaptan once a day (QD) compared with matching placebo in adults (18 years and older) with autism spectrum disorder (ASD)

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) guidelines according to the regulations and procedures described in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 January 2018
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: 241
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	France: 8
Worldwide total number of subjects	322
EEA total number of subjects	50

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)	322
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

322 Subjects were randomized. 1 subject did not receive the treatment and in the ITT Population, 321 subjects received at least one dose of the study treatment.

The Study was discontinued early before the planned sample size was reached.

Pre-assignment

Screening details:

Subjects subjects received matching placebo in Blinded Treatment Period for 24 Weeks and 10 mg of oral administration balovaptan once a day (QD) during the Open Label Extension Treatment Period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Balovaptan

Arm description:

Subjects received 10 mg of oral administration balovaptan once a day (QD).

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

Dosage and administration details:

10 mg of oral administration balovaptan once a day (QD).

Arm title	Placebo

Arm description:

Subjects received matching placebo in Blinded Treatment Period and 10 mg of oral administration balovaptan once a day (QD) in OLE Treatment period

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

Dosage and administration details:

Matching placebo

Number of subjects in period 1[1]	Balovaptan	Placebo
Started	163	158
Completed	103	102
Not completed	60	56
Consent withdrawn by subject	12	9
Physician decision	1	-
Adverse event, non-fatal	4	4
Study terminated by sponsor	39	34
Non-compliance with study drug	-	1
Lost to follow-up	1	4
Unable due to relocation, withdrawals, a partner	1	3
Protocol deviation	1	-
Lack of efficacy	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 1 Subjects was not involved in the treatment start.

Period 2

Period 2 title	Open Label Extension Treatment Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Balovaptan

Arm description:

Subjects received 10 mg of oral administration balovaptan once a day (QD).

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

Dosage and administration details:

10 mg of oral administration balovaptan once a day (QD).

Arm title	Placebo

Arm description:

Subjects received matching placebo in Blinded Treatment Period and 10 mg of oral administration balovaptan once a day (QD) in OLE Treatment period

Arm type	Placebo

Investigational medicinal product name	Matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo

Number of subjects in period 2[2]	Balovaptan	Placebo
Started	100	97
Completed	0	0
Not completed	100	97
Consent withdrawn by subject	8	2
left country no interest withdrawal spouse unable	-	1
Adverse event, non-fatal	7	-
Study terminated by sponsor	81	88
Non-compliance with study drug	-	1
Lost to follow-up	1	4
Lack of efficacy	3	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The study was pre-maturely terminated therefore number of started subjects did not complete.

Baseline characteristics

Reporting groups	
Reporting group title	Balovaptan
Reporting group description:	
Subjects received 10 mg of oral administration balovaptan once a day (QD).	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo in Blinded Treatment Period and 10 mg of oral administration balovaptan once a day (QD) in OLE Treatment period	

Reporting group values	Balovaptan	Placebo	Total
Number of subjects	163	158	321
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	163	158	321
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	27.6	27.6	
standard deviation	± 9.7	± 9.8	-
Sex: Female, Male Units: Subject			
Female	35	30	65
Male	128	128	256
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	15	13	28
Not Hispanic or Latino	145	142	287
Unknown or Not Reported	3	3	6
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	2	2
Asian	3	5	8
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	9	6	15
White	143	140	283
More than one race	3	1	4
Unknown or Not Reported	5	4	9

End points

End points reporting groups

Reporting group title	Balovaptan
Reporting group description:	
Subjects received 10 mg of oral administration balovaptan once a day (QD).	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo in Blinded Treatment Period and 10 mg of oral administration balovaptan once a day (QD) in OLE Treatment period	
Reporting group title	Balovaptan
Reporting group description:	
Subjects received 10 mg of oral administration balovaptan once a day (QD).	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo in Blinded Treatment Period and 10 mg of oral administration balovaptan once a day (QD) in OLE Treatment period	

Primary: Change from baseline at Week 24 on the Vineland Adaptive Behavior Scales (Vineland-II) two-domain composite (2DC) score.

End point title	Change from baseline at Week 24 on the Vineland Adaptive Behavior Scales (Vineland-II) two-domain composite (2DC) score.[1]
End point description:	
Vineland™-II Adaptive Behavior Scales 2-Domain Composite (2DC) Score is defined as mean of the Communication domain standard score & Socialization domain standard score. If any of the 2 individual domain standard scores is missing 2DC score is not computed. Vineland™-II is an instrument that measures communication, daily living skills, socialization, motor skills and maladaptive behavior of individuals with developmental disabilities. Survey Interview Form will be administered to a subject's reliable study partner in this study, during which the rater or clinician will ask to the study partner open ended questions relating to the subject's activities and behavior. Standardized scores on the Adaptive behavior composite range from 20-160 with higher scores indicating better functioning.	
End point type	Primary
End point timeframe:	
Week 24 (Blinded Treatment Period)	

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: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Balovaptan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	99		
Units: Number				
arithmetic mean (standard deviation)	4.56 (± 10.85)	6.83 (± 12.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at Week 12 on the Vineland-II 2DC score

End point title	Change from baseline at Week 12 on the Vineland-II 2DC score

End point description:

Vineland™-II Adaptive Behavior Scales 2-Domain Composite (2DC) Score is defined as mean of the Communication domain standard score & Socialization domain standard score. If any of the 2 individual domain standard scores is missing 2DC score is not computed. Vineland™-II is an instrument that measures communication, daily living skills, socialization, motor skills and maladaptive behavior of individuals with developmental disabilities. Survey Interview Form will be administered to a subject's reliable study partner in this study, during which the rater or clinician will ask to the study partner open ended questions relating to the subject's activities and behavior. Standardized scores on the Adaptive behavior composite range from 20-160 with higher scores indicating better functioning.

End point type	Secondary

End point timeframe:

Week 12 (Blinded Treatment Period)

End point values	Balovaptan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	140		
Units: Number				
arithmetic mean (standard deviation)	3.47 (± 10.00)	4.85 (± 12.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at Weeks 12 and 24 in the Pediatric Quality of Life (PedsQL) Inventory Generic Core Scales, Version 4.0, on summary and total scores

End point title	Change from baseline at Weeks 12 and 24 in the Pediatric Quality of Life (PedsQL) Inventory Generic Core Scales, Version 4.0, on summary and total scores

End point description:

The Pediatric Quality of Life Inventory PedsQL™4.0 Generic Core Scale assessment consists of a 23 item questionnaire encompassing 4 core scale domains: Physical Functioning (8 items); Emotional Functioning (5 items); Social Functioning (5 items); and School Functioning (5 items). Items are scored on a 5 point Likert-type response scale (0=never a problem; 1=almost never a problem; 2=sometimes a problem; 3=often a problem; and 4=almost always a problem). Once scored, items will be reverse scored and linearly transformed to a 0-100 scale (0=100, 1=75, 2=50, 3=25, 4=0), so that higher scores indicate better health-related quality of life.

End point type	Secondary

End point timeframe:

Weeks 12 and 24 (Blinded Treatment Period)

End point values	Balovaptan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163[2]	158[3]		
Units: Number				
arithmetic mean (standard deviation)				
Week 12 Total Score	4.1 (± 11.2)	5.0 (± 10.2)		
Week 12 Psychosocial Health Summary	4.9 (± 13.2)	5.5 (± 12.7)		
Week 12 Physical Health Summary	2.5 (± 13.3)	4.3 (± 12.3)		
Week 24 Total Score	8.0 (± 13.7)	6.0 (± 11.6)		
Week 24 Psychosocial Health Summary	10.0 (± 15.4)	6.9 (± 14.1)		
Week 24 Physical Health Summary	4.3 (± 15.5)	4.4 (± 14.5)		

Notes:

[2] - Subject number analyzed
Week 12-144
Week 24-106
[3] - Subject number analyzed
Week 12-124, but 125 for psychosocial health
Week 24-92

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at Weeks 12 and 24 in the Vineland-II adaptive behavior composite standard score

End point title	Change from baseline at Weeks 12 and 24 in the Vineland-II adaptive behavior composite standard score

End point description:

The Vineland-II is an instrument that measures communication, daily living skills, socialization, motor skills (only in children up to 6 years) and maladaptive (not assessed in this study) behavior of individuals with developmental disabilities. The Survey Interview Form (i.e., semi -structured interview) will be administered to a subject's reliable study partner in this study, during which the rater or clinician will ask to the study partner open ended questions relating to the subject's activities and behavior. Domain scores will be obtained for the individual domains of Socialization, Communication, Daily Living Skills, and motor skills (up to 6 years only) and used to calculate the Vineland-II Adaptive Behavior Composite score. Standardized scores on the Adaptive behavior composite range from 20-160 with higher scores indicating better functioning. Only descriptive statistics presented instead of the planned estimated due to the early discontinuation of the study due to futility.

End point type	Secondary

End point timeframe:

Weeks 12 and 24 (Blinded Treatment Period)

End point values	Balovaptan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163[4]	158[5]		
Units: Number				
arithmetic mean (standard deviation)				
Change from baseline Week 12	2.87 (± 6.99)	3.99 (± 10.01)		
Change from baseline Week 24	4.32 (± 8.43)	5.26 (± 9.69)		

Notes:

[4] - Subject number analyzed
Week 12-150
Week 24-111

[5] - Subject number analyzed
Week 12-140
Week 24-99

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at Week 12 and 24 on the Vineland-II Socialization domain standard score

End point title	Change from baseline at Week 12 and 24 on the Vineland-II Socialization domain standard score

End point description:

The Vineland-II is an instrument that measures communication, daily living skills, socialization, motor skills (only in children up to 6 years) and maladaptive (not assessed in this study) behavior of individuals with developmental disabilities. The Survey Interview Form (i.e., semi -structured interview) will be administered to a subject's reliable study partner in this study, during which the rater or clinician will ask to the study partner open ended questions relating to the subject's activities and behavior. Domain scores will be obtained for the individual domains of Socialization, Communication, Daily Living Skills, and motor skills (up to 6 years only) and used to calculate the Vineland-II Adaptive Behavior Composite score. Standardized scores on the Adaptive behavior composite range from 20-160 with higher scores indicating better functioning.

Only descriptive statistics presented instead of the planned estimand due to the early discontinuation of the study due to futility.

End point type	Secondary

End point timeframe:

Weeks 12 and 24 (Blinded Treatment Period)

End point values	Balovaptan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163[6]	158[7]		
Units: Number				
arithmetic mean (standard deviation)				
Week 12	3.63 (± 11.58)	5.26 (± 12.71)		
Week 24	5.54 (± 13.54)	6.86 (± 11.75)		

Notes:

[6] - Subject number analyzed
Week 12-150
Week 24-111

[7] - Subject number analyzed
Week 12-140
Week 24-99

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at Weeks 12 and 24 on the Vineland-II Communication domain standard score

End point title	Change from baseline at Weeks 12 and 24 on the Vineland-II Communication domain standard score

End point description:

The Vineland-II is an instrument that measures communication, daily living skills, socialization, motor skills (only in children up to 6 years) and maladaptive (not assessed in this study) behavior of individuals with developmental disabilities. The Survey Interview Form (i.e., semi -structured interview) will be administered to a subject's reliable study partner in this study, during which the rater or clinician will ask to the study partner open ended questions relating to the subject's activities and behavior. Domain scores will be obtained for the individual domains of Socialization, Communication, Daily Living Skills, and motor skills (up to 6 years only) and used to calculate the Vineland-II Adaptive Behavior Composite score. Standardized scores on the Adaptive behavior composite range from 20-160 with higher scores indicating better functioning.

End point type	Secondary

End point timeframe:

Weeks 12 and 24 (Blinded Treatment Period)

End point values	Balovaptan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163[8]	158[9]		
Units: Number				
arithmetic mean (standard deviation)				
Week 12	3.30 (± 13.74)	4.44 (± 16.58)		
Week 24	3.59 (± 16.30)	6.81 (± 17.50)		

Notes:

[8] - Subject number analyzed
Week 12-150
Week 24-111

[9] - Subject number analyzed
Week 12-150
Week 24-111

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at Weeks 12 and 24 on the Vineland-II Daily Living Skills domain standard score

End point title	Change from baseline at Weeks 12 and 24 on the Vineland-II Daily Living Skills domain standard score

End point description:

The Vineland-II is an instrument that measures communication, daily living skills, socialization, motor skills (only in children up to 6 years) and maladaptive (not assessed in this study) behavior of individuals with developmental disabilities. The Survey Interview Form (i.e., semi -structured interview) will be administered to a subject's reliable study partner in this study, during which the rater or clinician will ask to the study partner open ended questions relating to the subject's activities and behavior. Domain scores will be obtained for the individual domains of Socialization, Communication, Daily Living Skills, and motor skills (up to 6 years only) and used to calculate the Vineland-II Adaptive Behavior Composite score. Standardized scores on the Adaptive behavior composite range from 20-160 with higher scores indicating better functioning. Only descriptive statistics presented due to the early discontinuation of the study due to futility.

End point type	Secondary

End point timeframe:

Weeks 12 and 24 (Blinded Treatment Period)

End point values	Balovaptan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163[10]	158[11]		
Units: Number				
arithmetic mean (standard deviation)				
Week 12	2.93 (± 8.44)	2.74 (± 9.20)		
Week 24	5.14 (± 9.34)	3.02 (± 9.04)		

Notes:

[10] - Subject number analyzed
Week 12-150
Week 24-111
[11] - Subject number analyzed
Week 12-140
Week 24-99

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in severity of clinical impressions as measured by Clinical Global Impression-Severity (CGI-S)

End point title	Change from baseline in severity of clinical impressions as measured by Clinical Global Impression-Severity (CGI-S)

End point description:

The CGI-S reflects the rater's impression of the subject's current autism severity on a 7-point scale ranging from no symptoms (1) to very severe symptoms (7). Changes in CGI-S score were calculated as increase or decrease in absolute CGI-S scores between Baseline and Weeks 12 and 24.

End point type	Secondary

End point timeframe:

Weeks 12 and 24 (Blinded Treatment Period)

End point values	Balovaptan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163[12]	158[13]		
Units: Subjects				
number (not applicable)				
Week 12 -3	0	0		
Week 12 -2	3	3		
Week 12 -1	32	34		
Week 12 0	110	98		
Week 12 +1	1	1		
Week 12 +2	1	0		
Week 12 +3	0	0		
Week 24 -3	0	1		
Week 24 -2	6	10		
Week 24 -1	30	20		
Week 24 0	72	68		
Week 24 +1	1	1		
Week 24 +2	0	0		
Week 24 +3	0	0		

Notes:

[12] - Subject number analyzed
Week 12-147
Week 24-109
[13] - Subject number analyzed
Week 12-136
Week 24-100

Statistical analyses

No statistical analyses for this end point

Secondary: Improvements in clinical impressions, as measured by Clinical Global Impression-Improvement (CGI-I)

End point title	Improvements in clinical impressions, as measured by Clinical Global Impression-Improvement (CGI-I)

End point description:

This is a 7-point Likert scale that assesses improvement of the patient's condition. Scores range from the worst score of 7 (Very much worse) to the best score of 1 (Very much improved). Lower scores are better on this scale, and indicate greater improvement.

End point type	Secondary

End point timeframe:

Weeks 12 and 24 (Blinded Treatment Period)

End point values	Balovaptan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163[14]	158[15]		
Units: Number				
number (not applicable)				
Week 12 1 Very much improved	0	0		
Week 12 2 Much improved	15	20		
Week 12 3 Minimally improved	54	59		
Week 12 4 No change	74	56		
Week 12 5 Minimally worse	5	1		
Week 12 6 Much worse	0	0		
Week 12 7 Very much worse	0	0		
Week 24 1 Very much improved	0	2		
Week 24 2 Much improved	17	24		
Week 24 3 Minimally improved	48	40		
Week 24 4 No change	42	33		
Week 24 5 Minimally worse	1	1		
Week 24 6 Much worse	1	0		
Week 24 7 Very much worse	0	0		

Notes:

[14] - Subject number analyzed
Week 12-148
Week 24-109
[15] - Subject number analyzed
Week 12-136
Week 24-100

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at Weeks 12 and 24 in the Hamilton Anxiety Rating Scale (HAM-A) total and domain scores

End point title	Change from baseline at Weeks 12 and 24 in the Hamilton Anxiety Rating Scale (HAM-A) total and domain scores

End point description:

The HAM-A is a 14-item, rater administered interview, assessing the severity of anxiety symptoms during the past 7 days. Seven items assess psychic anxiety and seven assess somatic anxiety. Each item utilizes a 5-point symptom severity response scale, ranging from none (0) to very severe (4). A total score is calculated that ranges from 0 to 56; higher scores are indicative of more severe anxiety.

End point type	Secondary

End point timeframe:

Weeks 12 and 24 (Blinded Treatment Period)

End point values	Balovaptan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163[16]	158[17]		
Units: Number				
arithmetic mean (standard deviation)				
Week 12 Total	-1.7 (± 4.9)	-2.8 (± 4.4)		
Week 12 Psychic Anxiety Subscale	-1.3 (± 3.5)	-1.8 (± 3.2)		
Week 12 Somatic Anxiety Subscale	-0.4 (± 2.4)	-1.0 (± 2.5)		
Week 24 Total	-2.7 (± 4.5)	-2.8 (± 5.7)		
Week 24 Psychic Anxiety Subscale	-2.1 (± 3.4)	-1.8 (± 3.9)		
Week 24 Somatic Anxiety Subscale	-0.6 (± 2.2)	-1.0 (± 2.9)		

Notes:

[16] - Subject number analyzed
Week 12-153
Week 24-115
[17] - Subject number analyzed
Week 12-143
Week 24-104

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with a >=6-point improvement in Vineland-II 2DC score

End point title	Proportion of subjects with a >=6-point improvement in Vineland-II 2DC score

End point description:

Vineland™-II Adaptive Behavior Scales 2-Domain Composite (2DC) Score is defined as mean of the Communication domain standard score & Socialization domain standard score. If any of the 2 individual domain standard scores is missing 2DC score is not computed. Vineland™-II is an instrument that measures communication, daily living skills, socialization, motor skills and maladaptive behavior of individuals with developmental disabilities. Survey Interview Form will be administered to a subject's reliable study partner in this study, during which the rater or clinician will ask to the study partner open ended questions relating to the subject's activities and behavior. Standardized scores on the Adaptive behavior composite range from 20-160 with higher scores indicating better functioning.

All participants who have an improvement of at least 6 points are included in the >=6 score threshold

End point type	Secondary

End point timeframe:

Weeks 12 and 24 (Blinded Treatment Period)

End point values	Balovaptan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163[18]	158[19]		
Units: Percentage of Subjects				
number (not applicable)				
Week 12	34.4	42.1		
Week 24	43.0	48.4		

Notes:

[18] - Subject number analyzed
Week 12-128
Week 24-100
[19] - Subject number analyzed
Week 12-114
Week 24-93

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with adverse events

End point title	Percentage of subjects with adverse events

End point description:

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. The Blinded Treatment Period continued for 24 weeks, Open Label Extension (OLE) Treatment Period continued up to 2 years. The study was pre-maturely terminated, therefore did not reach the planned end date.

End point type	Secondary

End point timeframe:

Week 24 and Up to Approximately 2 Years

End point values	Balovaptan	Balovaptan	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	163	100	158	97[20]
Units: Percentage of Subjects				
number (not applicable)	60.1	59.0	65.8	55.7

Notes:

[20] - Subjects received placebo in blinded and 10mg balovaptan daily in open label treatment period

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline to the end of Safety Period, up to 2 years	
Adverse event reporting additional description:	
In the Open Label Extension (OLE) Treatment Period, the subjects received active treatment, i.e. 10mg balovaptan QD. Placebo was only given during the blinded treatment period but not during OLE Treatment Period. Other Adverse Events are reported at 5% frequency threshold.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Balovaptan in Blinded Treatment Period
Reporting group description:	
Subjects 10 mg of oral administration balovaptan once a day (QD).	
Reporting group title	Placebo Blinded Treatment Period
Reporting group description:	
Subjects received matching placebo.	
Reporting group title	Balovaptan in Open Label Extension Treatment Period
Reporting group description:	
Subjects received 10 mg of oral administration balovaptan once a day (QD).	
Reporting group title	Placebo in Open Label Extension Treatment Period
Reporting group description:	
Subjects received matching placebo in Blinded Treatment Period and 10 mg of oral administration balovaptan once a day (QD). OLE Treatment Period	

Serious adverse events	Balovaptan in Blinded Treatment Period	Placebo Blinded Treatment Period	Balovaptan in Open Label Extension Treatment Period
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 163 (1.23%)	5 / 158 (3.16%)	0 / 100 (0.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 163 (0.00%)	0 / 158 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			

subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Schizoaffective disorder			
subjects affected / exposed	1 / 163 (0.61%)	0 / 158 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	1 / 163 (0.61%)	1 / 158 (0.63%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic disorder			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed suicide			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 163 (0.00%)	1 / 158 (0.63%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 163 (0.00%)	0 / 158 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis streptococcal			

subjects affected / exposed	0 / 163 (0.00%)	0 / 158 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 163 (0.00%)	0 / 158 (0.00%)	0 / 100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo in Open Label Extension Treatment Period		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 97 (2.06%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Schizoaffective disorder			
subjects affected / exposed	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Panic disorder			

subjects affected / exposed	0 / 97 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Completed suicide				
subjects affected / exposed	0 / 97 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abscess limb				
subjects affected / exposed	0 / 97 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	0 / 97 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis streptococcal				
subjects affected / exposed	1 / 97 (1.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 97 (1.03%)			
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	Balovaptan in Blinded Treatment Period	Placebo Blinded Treatment Period	Balovaptan in Open Label Extension Treatment Period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 163 (30.06%)	59 / 158 (37.34%)	28 / 100 (28.00%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 163 (1.23%)	10 / 158 (6.33%)	2 / 100 (2.00%)
occurrences (all)	2	10	2
Headache			
subjects affected / exposed	8 / 163 (4.91%)	7 / 158 (4.43%)	5 / 100 (5.00%)
occurrences (all)	13	9	5
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 163 (6.75%)	14 / 158 (8.86%)	5 / 100 (5.00%)
occurrences (all)	15	15	5
Nausea			
subjects affected / exposed	4 / 163 (2.45%)	7 / 158 (4.43%)	1 / 100 (1.00%)
occurrences (all)	4	8	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	5 / 163 (3.07%)	8 / 158 (5.06%)	0 / 100 (0.00%)
occurrences (all)	5	8	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	8 / 163 (4.91%)	7 / 158 (4.43%)	8 / 100 (8.00%)
occurrences (all)	11	7	8
Insomnia			
subjects affected / exposed	5 / 163 (3.07%)	8 / 158 (5.06%)	3 / 100 (3.00%)
occurrences (all)	5	8	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 163 (8.59%)	19 / 158 (12.03%)	7 / 100 (7.00%)
occurrences (all)	14	22	10
Upper respiratory tract infection			
subjects affected / exposed	10 / 163 (6.13%)	9 / 158 (5.70%)	6 / 100 (6.00%)
occurrences (all)	13	11	7
Gastroenteritis			

subjects affected / exposed	2 / 163 (1.23%)	0 / 158 (0.00%)	1 / 100 (1.00%)
occurrences (all)	2	0	1

Non-serious adverse events	Placebo in Open Label Extension Treatment Period		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 97 (30.93%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	10 / 97 (10.31%)		
occurrences (all)	17		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 97 (4.12%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	3 / 97 (3.09%)		
occurrences (all)	3		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 97 (3.09%)		
occurrences (all)	4		
Insomnia			
subjects affected / exposed	3 / 97 (3.09%)		
occurrences (all)	3		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 97 (4.12%)		
occurrences (all)	4		
Upper respiratory tract infection			

subjects affected / exposed	7 / 97 (7.22%)		
occurrences (all)	11		
Gastroenteritis			
subjects affected / exposed	5 / 97 (5.15%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2019	Protocol WN39434 has been amended primarily to update the requirements for cardiac monitoring in response to specific requests received from the U.S. Food and Drug Administration (FDA) and to remove the capillary blood draw option.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
04 March 2020	The study is pre-maturely terminated without a restart date, futility analysis decision.	-

Notes:

Limitations and caveats

None reported