Clinical trial results:
A Phase II Multi-Center, Randomized, Double-Blind, 24-Week, Parallel Group, Placebo-Controlled Study to Investigate the Efficacy and Safety of Balovaptan (RO5285119) in Children and Adolescents Age 5-17 With Autism Spectrum Disorder (ASD)

Summary

EudraCT number	2020-003173-22
Trial protocol	Outside EU/EEA
Global end of trial date	30 June 2020

Results information

Result version number	v1 (current)
This version publication date	23 December 2020
First version publication date	23 December 2020

Trial information

Trial identification

Sponsor protocol code	BP30153

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02901431
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001918-PIP01-15
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	30 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 June 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to evaluate the efficacy of 24-week treatment with balovaptan (RO5285119) 10 mg equivalent compared to placebo as measured by the change from baseline on the Vineland™-II Adaptive Behavior Scales, second edition (Vineland™-II) Two Domain Composite (2DC) (average of Communication and Socialization domains).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 339
Worldwide total number of subjects	339
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	127
Adolescents (12-17 years)	212
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 339 participants were enrolled from 44 sites in the United States.

Pre-assignment

Screening details:

For the Main Study Part and Open Extension Study Part, treatment groups were categorized based on the tertiles of individual participants PK exposure at Week 12. To allow clear analysis by exposure tertiles, participants with dose adjustment were excluded from the analysis by tertiles.

Period 1

Period 1 title	PK Part and Main Study Part
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	PK Part - Placebo

Arm description:

Participants received a matching placebo orally. Approximate treatment duration was up to 8 weeks.

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

Dosage and administration details:

Participants received a matching placebo orally. Approximate treatment duration was up to 8 weeks.

Arm title	PK Part - Balovaptan (RO5285119) 4 mg/d equivalent

Arm description:

Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 8 weeks.

Arm type	Experimental
Investigational medicinal product name	Balovaptan
Investigational medicinal product code	
Other name	RO5285119
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 8 weeks.

Arm title	PK Part - Balovaptan (RO5285119) 10 mg/d equivalent

Arm description:

Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 8 weeks.

Arm type	Experimental

Investigational medicinal product name	Balovaptan
Investigational medicinal product code	
Other name	RO5285119
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 8 weeks.

Arm title	Placebo

Arm description:

Participants received a matching placebo orally. Approximate treatment duration was up to 24 weeks in Main Study Part.

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

Dosage and administration details:

Participants received a matching placebo orally. Approximate treatment duration was up to 24 weeks in Main Study Part.

Arm title	Low Exposure Tertile

Arm description:

Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.

Arm type	Experimental
Investigational medicinal product name	Balovaptan
Investigational medicinal product code	
Other name	RO5285119
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment groups were categorized based on the tertiles of individual participant's PK exposure at week 12. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.

Arm title	Medium Exposure Tertile

Arm description:

Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.

Arm type	Experimental
Investigational medicinal product name	Balovaptan
Investigational medicinal product code	
Other name	RO5285119
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment groups were categorized based on the tertiles of individual participant's PK exposure at week 12. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.

Arm title	High Exposure Tertile

Arm description:

Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.

Arm type	Experimental
Investigational medicinal product name	Balovaptan
Investigational medicinal product code	
Other name	RO5285119
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment groups were categorized based on the tertiles of individual participant's PK exposure at week 12. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.

Arm title	Dose-Adjusters

Arm description:

Participants with dose adjustment who were excluded from the analysis by tertiles. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.

Arm type	Experimental
Investigational medicinal product name	Balovaptan
Investigational medicinal product code	
Other name	RO5285119
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Participants with dose adjustment who were excluded from the analysis by tertiles. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.

Number of subjects in period 1	PK Part - Placebo	PK Part - Balovaptan (RO5285119) 4 mg/d equivalent	PK Part - Balovaptan (RO5285119) 10 mg/d equivalent
Started	12	11	15
Completed	5	5	6
Not completed	7	6	9
Consent withdrawn by subject	1	1	3
Physician decision	-	-	-
Adverse event, non-fatal	-	1	-
Stopped treatment after 8 weeks	1	-	1
Discontinued per Sponsor	-	3	-
Pending IMC/SOC Dose Confirmation	2	-	-
Stopped per Sponsor pending dose confirmation	1	-	4
Lost to follow-up	-	-	1
Withdrawal by Caregiver	-	-	-

8 weeks of treatment ran out	2	-	-
Pending dose confirmation	-	1	-
Lack of efficacy	-	-	-

Number of subjects in period 1	Placebo	Low Exposure Tertile	Medium Exposure Tertile
Started	112	57	66
Completed	86	50	54
Not completed	26	7	12
Consent withdrawn by subject	18	3	5
Physician decision	1	-	-
Adverse event, non-fatal	3	3	4
Stopped treatment after 8 weeks	-	-	-
Discontinued per Sponsor	-	-	-
Pending IMC/SOC Dose Confirmation	-	-	-
Stopped per Sponsor pending dose confirmation	-	-	-
Lost to follow-up	3	1	2
Withdrawal by Caregiver	-	-	1
8 weeks of treatment ran out	-	-	-
Pending dose confirmation	-	-	-
Lack of efficacy	1	-	-

Number of subjects in period 1	High Exposure Tertile	Dose-Adjusters
Started	66	7
Completed	55	7
Not completed	11	0
Consent withdrawn by subject	6	-
Physician decision	1	-
Adverse event, non-fatal	1	-
Stopped treatment after 8 weeks	-	-
Discontinued per Sponsor	-	-
Pending IMC/SOC Dose Confirmation	-	-
Stopped per Sponsor pending dose confirmation	-	-
Lost to follow-up	3	-
Withdrawal by Caregiver	-	-
8 weeks of treatment ran out	-	-
Pending dose confirmation	-	-
Lack of efficacy	-	-

Period 2

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

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.

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

Dosage and administration details:

Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.

Arm title	Low Exposure Tertile

Arm description:

Tertiles were used as derived from the main study part at Week 12. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.

Arm type	Experimental
Investigational medicinal product name	Balovaptan
Investigational medicinal product code	
Other name	RO5285119
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment groups were categorized based on the tertiles of individual participant's PK exposure at week 12. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.

Arm title	Medium Exposure Tertile

Arm description:

Tertiles were used as derived from the main study part at Week 12. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.

Arm type	Experimental

Investigational medicinal product name	Balovaptan
Investigational medicinal product code	
Other name	RO5285119
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment groups were categorized based on the tertiles of individual participant's PK exposure at week 12. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.

Arm title	High Exposure Tertile

Arm description:

Tertiles were used as derived from the main study part at Week 12. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.

Arm type	Experimental
Investigational medicinal product name	Balovaptan
Investigational medicinal product code	
Other name	RO5285119
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment groups were categorized based on the tertiles of individual participant's PK exposure at week 12. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.

Arm title	Dose-Adjusters

Arm description:

Participants with dose adjustment who were excluded from the analysis by tertiles. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.

Arm type	Experimental
Investigational medicinal product name	Balovaptan
Investigational medicinal product code	
Other name	RO5285119
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Participants with dose adjustment who were excluded from the analysis by tertiles. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.

Number of subjects in period 2	Placebo	Low Exposure Tertile	Medium Exposure Tertile
Started	68	35	40
Completed	20	11	11
Not completed	48	24	29
Physician decision	1	1	-
Consent withdrawn by subject	6	5	7

Adverse event, non-fatal	4	4	-
Study Terminated By Sponsor	35	12	21
Lost to follow-up	2	2	1

Number of subjects in period 2	High Exposure Tertile	Dose-Adjusters
Started	46	5
Completed	7	2
Not completed	39	3
Physician decision	-	-
Consent withdrawn by subject	3	1
Adverse event, non-fatal	4	1
Study Terminated By Sponsor	31	-
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	PK Part - Placebo
Reporting group description:	
Participants received a matching placebo orally. Approximate treatment duration was up to 8 weeks.	
Reporting group title	PK Part - Balovaptan (RO5285119) 4 mg/d equivalent
Reporting group description:	
Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 8 weeks.	
Reporting group title	PK Part - Balovaptan (RO5285119) 10 mg/d equivalent
Reporting group description:	
Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 8 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received a matching placebo orally. Approximate treatment duration was up to 24 weeks in Main Study Part.	
Reporting group title	Low Exposure Tertile
Reporting group description:	
Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.	
Reporting group title	Medium Exposure Tertile
Reporting group description:	
Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.	
Reporting group title	High Exposure Tertile
Reporting group description:	
Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.	
Reporting group title	Dose-Adjusters
Reporting group description:	
Participants with dose adjustment who were excluded from the analysis by tertiles. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.	

Reporting group values	PK Part - Placebo	PK Part - Balovaptan (RO5285119) 4 mg/d equivalent	PK Part - Balovaptan (RO5285119) 10 mg/d equivalent
Number of subjects	12	11	15
Age categorical Units: Subjects			

Age Continuous			
Participants in the PK part and Main Study Part.			
Units: years			
arithmetic mean	8.9	9.9	10.4
standard deviation	± 3.8	± 3.3	± 3.5

Sex: Female, Male			
The overall total numbers of baseline participants is lower than the sum of the groups because 7 re-starters are counted in both the PK part and Main Study Part of the study.			
Units: Participants			
Female	3	1	4
Male	9	10	11

Reporting group values	Placebo	Low Exposure Tertile	Medium Exposure Tertile
Number of subjects	112	57	66
Age categorical			
Units: Subjects			

Age Continuous			
Participants in the PK part and Main Study Part.			
Units: years			
arithmetic mean	12.5	13.3	12.6
standard deviation	± 3.0	± 2.3	± 3.0
Sex: Female, Male			
The overall total numbers of baseline participants is lower than the sum of the groups because 7 re-starters are counted in both the PK part and Main Study Part of the study.			
Units: Participants			
Female	17	9	8
Male	95	48	58

Reporting group values	High Exposure Tertile	Dose-Adjusters	Total
Number of subjects	66	7	346
Age categorical			
Units: Subjects			

Age Continuous			
Participants in the PK part and Main Study Part.			
Units: years			
arithmetic mean	11.8	12.6	
standard deviation	± 3.3	± 2.1	-
Sex: Female, Male			
The overall total numbers of baseline participants is lower than the sum of the groups because 7 re-starters are counted in both the PK part and Main Study Part of the study.			
Units: Participants			
Female	11	0	53
Male	55	7	293

End points

End points reporting groups

Reporting group title	PK Part - Placebo
Reporting group description:	
Participants received a matching placebo orally. Approximate treatment duration was up to 8 weeks.	
Reporting group title	PK Part - Balovaptan (RO5285119) 4 mg/d equivalent
Reporting group description:	
Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 8 weeks.	
Reporting group title	PK Part - Balovaptan (RO5285119) 10 mg/d equivalent
Reporting group description:	
Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 8 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received a matching placebo orally. Approximate treatment duration was up to 24 weeks in Main Study Part.	
Reporting group title	Low Exposure Tertile
Reporting group description:	
Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.	
Reporting group title	Medium Exposure Tertile
Reporting group description:	
Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.	
Reporting group title	High Exposure Tertile
Reporting group description:	
Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.	
Reporting group title	Dose-Adjusters
Reporting group description:	
Participants with dose adjustment who were excluded from the analysis by tertiles. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.	
Reporting group title	Placebo
Reporting group description:	
Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.	
Reporting group title	Low Exposure Tertile
Reporting group description:	
Tertiles were used as derived from the main study part at Week 12. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.	
Reporting group title	Medium Exposure Tertile
Reporting group description:	
Tertiles were used as derived from the main study part at Week 12. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension	

Part.

Reporting group title	High Exposure Tertile

Reporting group description:

Tertiles were used as derived from the main study part at Week 12. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.

Reporting group title	Dose-Adjusters

Reporting group description:

Participants with dose adjustment who were excluded from the analysis by tertiles. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.

Subject analysis set title	PK Part - Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received a matching placebo orally. Approximate treatment duration was up to 8 weeks.

Subject analysis set title	PK Part - Balovaptan (RO5285119) 4 mg/d equivalent
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 8 weeks.

Subject analysis set title	PK Part - Balovaptan (RO5285119) 10 mg/d equivalent
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 mg/d of balovaptan (RO5285119). Approximate treatment duration was up to 8 weeks.

Subject analysis set title	Main Study Part - Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants in the Main Study Part received a matching placebo orally. Approximate treatment duration was up to 24 weeks.

Subject analysis set title	Main Study Part - Low Exposure Tertile
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Main Study Part in the Low Exposure Tertile received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Assignment to tertile groups was based on week 12 PK exposure. Approximate treatment duration was up to 24 weeks.

Subject analysis set title	Main Study Part - Medium Exposure Tertile
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Main Study Part in the Medium Exposure Tertile received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Assignment to tertile groups was based on week 12 PK exposure. Approximate treatment duration was up to 24 weeks.

Subject analysis set title	Main Study Part - High Exposure Tertile
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Main Study Part in the High Exposure Tertile received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Assignment to tertile groups was based on week 12 PK exposure. Approximate treatment duration was up to 24 weeks.

Subject analysis set title	Main Study Part - Dose-Adjusters
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with dose adjustment who were excluded from the analysis by tertiles. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.

Subject analysis set title	Main Study Part, Low Exposure Tertile
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Main Study Part in the Low Exposure Tertile received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks.

Subject analysis set title	Main Study Part, Medium Exposure Tertile
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Main Study Part in the Medium Exposure Tertile received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks.

Subject analysis set title	Main Study Part, High Exposure Tertile
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Main Study Part in the High Exposure Tertile received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks.

Subject analysis set title	Main Study Part - All Treated
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants in the Main Study Part received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). This group includes participants from the low, medium, and high exposure tertiles, as well as the Dose-Adjusters. Approximate treatment duration was up to 24 weeks.

Subject analysis set title	Open Label Extension Part, Low Exposure Tertile
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Open Label Extension Part of the study in the Low Exposure Tertile received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks.

Subject analysis set title	Open Label Extension Part, Medium Exposure Tertile
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Open Label Extension Part of the study in the Medium Exposure Tertile received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.

Subject analysis set title	Open Label Extension Part, High Exposure Tertile
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in the Open Label Extension Part of the study in the High Exposure Tertile received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up 52 weeks.

Subject analysis set title	Open Label Extension Part, All Treated
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All participants in the Open Label Extension Part of the study received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). This group includes participants from the low, medium, and high exposure tertiles, as well as the Dose-Adjusters. Approximate treatment duration was up to 52 weeks.

Subject analysis set title	Efficacy Inferential - Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subset of the Efficacy Population used for analyses of primary and secondary efficacy endpoints. It was divided by randomized treatment and included patients taking balovaptan 10 mg eq dose and patients from the concurrently randomized PBO group in the corresponding randomization stage. Patients with dose adjustments or interruptions, or who were on a different dose than the final dose for their age group, were excluded.

Subject analysis set title	Efficacy Inferential - Balovaptan 10 mg/d equivalent
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subset of the Efficacy Population used for analyses of primary and secondary efficacy endpoints. It was divided by randomized treatment and included patients taking balovaptan 10 mg eq dose and patients from the concurrently randomized PBO group in the corresponding randomization stage. Patients with dose adjustments or interruptions, or who were on a different dose than the final dose for their age group, were excluded.

Primary: Change From Baseline in Vineland™-II Adaptive Behavior Scale Two Domain Composite (2DC) Score at Week 24 for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

End point title	Change From Baseline in Vineland™-II Adaptive Behavior Scale Two Domain Composite (2DC) Score at Week 24 for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

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 caregiver in this study, during which the rater or clinician will ask to the caregiver 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. Mixed model with repeated measures (MMRM) was used for analysis with assessments at baseline, Week 12 and Week 24.

End point type	Primary

End point timeframe:

Baseline, Week 24

End point values	Efficacy Inferential - Placebo	Efficacy Inferential - Balovaptan 10 mg/d equivalent		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	86		
Units: Score on a scale				
least squares mean (standard error)	2.34 (± 1.15)	2.17 (± 1.11)		

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

Mixed Model Repeat Measurements (MMRM) was applied.

Comparison groups	Efficacy Inferential - Placebo v Efficacy Inferential - Balovaptan 10 mg/d equivalent

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.911
Method	Mixed models analysis
Parameter estimate	Difference in Adjusted LSMeans
Point estimate	-0.16
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.56
upper limit	2.23

Secondary: Change from Baseline in Vineland™-II Composite Standard Score After 12 Weeks and 24 Weeks of Treatment for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

End point title	Change from Baseline in Vineland™-II Composite Standard Score After 12 Weeks and 24 Weeks of Treatment for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

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 caregiver in this study, during which the rater or clinician will ask to the caregiver 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:

Baseline, Weeks 12 and 24

End point values	Efficacy Inferential - Placebo	Efficacy Inferential - Balovaptan 10 mg/d equivalent		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	86		
Units: Score on a scale				
least squares mean (standard error)				
Week 12	1.45 (± 1.07)	1.74 (± 1.04)		
Week 24	2.20 (± 1.19)	1.97 (± 1.15)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Statistical analysis description: Week 12	
Comparison groups	Efficacy Inferential - Placebo v Efficacy Inferential - Balovaptan 10 mg/d equivalent
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in adjused LSMean
Point estimate	0.29
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.85
upper limit	2.43

Statistical analysis title	Statistical Analysis
Statistical analysis description: Week 24	
Comparison groups	Efficacy Inferential - Placebo v Efficacy Inferential - Balovaptan 10 mg/d equivalent
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in adjusted LSMean
Point estimate	-0.23
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.67
upper limit	2.22

Secondary: Change From Baseline in Vineland™-II Adaptive Behavior Scale Communication, Socialization, and Daily Living Skills Domain Standard Scores at Weeks 12 and 24 for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

End point title	Change From Baseline in Vineland™-II Adaptive Behavior Scale Communication, Socialization, and Daily Living Skills Domain Standard Scores at Weeks 12 and 24 for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

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 caregiver in this study, during which the rater or clinician will ask to the caregiver open ended questions relating to the subject's activities and behavior. Domain scores will be obtained for the individual domains of Socialization, Communication, and Daily Living Skills. Standardized scores on the Adaptive behavior composite range from 20-160 with higher scores indicating better functioning. Measure Type is Adjusted least-squares means.

End point type	Secondary

End point timeframe:
Baseline, Weeks 12 and 24

End point values	Efficacy Inferential - Placebo	Efficacy Inferential - Balovaptan 10 mg/d equivalent		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	86		
Units: Score on a scale				
least squares mean (standard error)				
Communication Domain Standard Score, Week 12	1.86 (± 1.06)	1.64 (± 1.03)		
Communication Domain Standard Score, Week 24	1.51 (± 1.13)	2.21 (± 1.09)		
Socialization Domain Standard Score, Week 12	1.69 (± 1.31)	2.20 (± 1.26)		
Socialization Domain Standard Score, Week 24	2.87 (± 1.50)	2.26 (± 1.45)		
Daily Living Skills Domain Standard Score, Week 12	-0.01 (± 1.38)	2.13 (± 1.35)		
Daily Living Skills Domain Standard Score, Week 24	1.44 (± 1.49)	1.61 (± 1.45)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Statistical analysis description:	
Communication Domain Standard Score, Week 12	
Comparison groups	Efficacy Inferential - Placebo v Efficacy Inferential - Balovaptan 10 mg/d equivalent
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in adjusted LSMean
Point estimate	-0.22
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.36
upper limit	1.92

Statistical analysis title	Statistical Analysis
Statistical analysis description:	
Communication Domain Standard Score, Week 24	
Comparison groups	Efficacy Inferential - Placebo v Efficacy Inferential - Balovaptan 10 mg/d equivalent

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in adjusted LSMean
Point estimate	0.71
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.6
upper limit	3.02

Statistical analysis title	Statistical Analysis
Statistical analysis description:	
Socialization Domain Standard Score, Week 12	
Comparison groups	Efficacy Inferential - Placebo v Efficacy Inferential - Balovaptan 10 mg/d equivalent
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in adjusted LSMean
Point estimate	0.51
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.1
upper limit	3.12

Statistical analysis title	Statistical Analysis
Comparison groups	Efficacy Inferential - Placebo v Efficacy Inferential - Balovaptan 10 mg/d equivalent
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	Difference in adjusted LSMean
Point estimate	-0.61
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.74
upper limit	2.51

Notes:

[1] - Socialization Domain Standard Score, Week 24

Statistical analysis title	Statistical Analysis
Comparison groups	Efficacy Inferential - Placebo v Efficacy Inferential - Balovaptan 10 mg/d equivalent

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority[2]
Parameter estimate	Difference in adjusted LSMean
Point estimate	2.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.63
upper limit	4.9

Notes:

[2] - Daily Living Skills Domain Standard Score, Week 12

Statistical analysis title	Statistical Analysis
Comparison groups	Efficacy Inferential - Placebo v Efficacy Inferential - Balovaptan 10 mg/d equivalent
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority[3]
Parameter estimate	Differences in adjusted LSMean
Point estimate	0.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.87
upper limit	3.22

Notes:

[3] - Daily Living Skills Domain Standard Score, Week 24

Secondary: Proportion of Subjects with >=6 Points Improvement in the Vineland-II 2DC Score for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

End point title	Proportion of Subjects with >=6 Points Improvement in the Vineland-II 2DC Score for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

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 caregiver in this study, during which the rater or clinician will ask to the caregiver 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 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:

Baseline, Weeks 12 and 24

End point values	Efficacy Inferential - Placebo	Efficacy Inferential - Balovaptan 10 mg/d equivalent		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66[4]	70[5]		
Units: Percentage of participants				
number (not applicable)				
Week 12	30.3	27.1		
Week 24	34.4	32.8		

Notes:

[4] - Week 12, n=66 Week 24, n=61

[5] - Week 12, n=70 Week 24, n=67

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impressions-Severity (CGI-S) Score at Weeks 12 and 24 for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

End point title	Change From Baseline in Clinical Global Impressions-Severity (CGI-S) Score at Weeks 12 and 24 for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

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).

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24

End point values	Efficacy Inferential - Placebo	Efficacy Inferential - Balovaptan 10 mg/d equivalent		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	67[6]	74[7]		
Units: Percentage of participants				
number (not applicable)				
-3 (Very much improved), Week 12	1.5	0		
-2 (Much improved), Week 12	1.5	2.7		
-1 (Minimally improved), Week 12	31.3	31.1		
0 (No change), Week 12	65.7	63.5		
+1 (Minimally worse), Week 12	0	2.7		
+2 (Much worse), Week 12	0	0		
+3 (Very Much worse), Week 12	0	0		
-3 (Very much improved), Week 24	1.6	0		
-2 (Much improved), Week 24	6.5	4.3		
-1 (Minimally improved), Week 24	32.3	31.9		
0 (No change), Week 24	59.7	63.8		
+1 (Minimally worse), Week 24	0	0		

+2 (Much worse), Week 24	0	0		
+3 (Very much worse), Week 24	0	0		

Notes:

[6] - Week 12, n=67 Week 24, n=62

[7] - Week 12, n=74 Week 24, n=69

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Ohio Autism Clinical Impressions Scale-Severity (OACIS-S) Score at Weeks 12 and 24 for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

End point title	Change From Baseline in Ohio Autism Clinical Impressions Scale-Severity (OACIS-S) Score at Weeks 12 and 24 for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

End point description:

The OACIS-S is a 10-item, clinician-completed measures based upon interview and/or observation. The OACIS-S assess severity and improvement, respectively, in social interaction, aberrant behavior, repetitive or ritualistic behavior, verbal communication, nonverbal communication skills, hyperactivity and inattention, anxiety and fearfulness, sensory sensitivities, restricted and narrow interests, and a global rating of autism. Each item of the OACIS-S is rated on a 7-point scale ranging from no symptoms (1) to very severe symptoms (7).

End point type	Secondary

End point timeframe:

Baseline, Weeks 12 and 24

End point values	Efficacy Inferential - Placebo	Efficacy Inferential - Balovaptan 10 mg/d equivalent		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	67[8]	73[9]		
Units: Percentage of participants				
number (not applicable)				
-3 (Very much improved), Week 12	3.0	0		
-2 (Much improved), Week 12	6.0	6.8		
-1 (Minimally improved), Week 12	28.4	34.2		
0 (No change), Week 12	59.7	57.5		
+1 (Minimally worse), Week 12	3.0	1.4		
+2 (Much worse), Week 12	0	0		
+3 (Very much worse), Week 12	0	0		
-3 (Very much improved), Week 24	6.5	0		
-2 (Much improved), Week 24	8.1	7.5		
-1 (Minimally improved), Week 24	33.9	28.4		
0 (No change), Week 24	48.4	61.2		
+1 (Minimally worse), Week 24	3.2	3.0		
+2 (Much worse), Week 24	0	0		
+3 (Very much worse), Week 24	0	0		

Notes:

[8] - Week 12, n=67 Week 24, n=62

[9] - Week 12, n=73 Week 24, n=67

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions- Improvement (CGI-I) Score at Weeks 12 and 24 for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

End point title	Clinical Global Impressions- Improvement (CGI-I) Score at Weeks 12 and 24 for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

End point description:

The CGI rating scales are tools used to evaluate both the severity of illness and change from baseline. The CGI-I is used to assess the clinical change as compared to symptoms at baseline using a 7-point scale, ranging from very much improved (1) to very much worse (7). For this study modified versions will be used.

End point type	Secondary

End point timeframe:

Weeks 12 and 24

End point values	Efficacy Inferential - Placebo	Efficacy Inferential - Balovaptan 10 mg/d equivalent		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	67[10]	74[11]		
Units: Percentage of participants				
number (not applicable)				
1 - Very much improved, Week 12	0	0		
2 - Much improved, Week 12	22.4	21.6		
3 - Minimally improved, Week 12	49.3	35.1		
4 - No change, Week 12	22.4	43.2		
5 - Minimally worse, Week 12	6.0	0		
6 - Much worse, Week 12	0	0		
7 - Very much worse, Week 12	0	0		
1 - Very much improved, Week 24	0	4.4		
2 - Much improved, Week 24	30.6	26.5		
3 - Minimally improved, Week 24	48.4	30.9		
4 - No change, Week 24	19.4	36.8		
5 - Minimally worse, Week 24	1.6	1.5		
6 - Much worse, Week 24	0	0		
7 - Very much worse, Week 24	0	0		

Notes:

[10] - Week 12, n=67 Week 24, n=62

[11] - Week 12, n=74 Week 24, n=68

Statistical analyses

No statistical analyses for this end point

Secondary: Ohio Autism Clinical Impressions Scale- Improvement (OACIS-I) Score at Weeks 12 and 24 for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

End point title	Ohio Autism Clinical Impressions Scale- Improvement (OACIS-I) Score at Weeks 12 and 24 for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

End point description:

The OACIS-I is a 10-item, clinician-completed measures based upon interview and/or observation. The OACIS-I assess severity and improvement, respectively, in social interaction, aberrant behavior, repetitive or ritualistic behavior, verbal communication, nonverbal communication skills, hyperactivity and inattention, anxiety and fearfulness, sensory sensitivities, restricted and narrow interests, and a global rating of autism. The OACIS-I is used to assess the clinical change as compared to symptoms at baseline using a 7-point scale, ranging from very much improved (1) to very much worse (7).

End point type	Secondary

End point timeframe:

Weeks 12 and 24

End point values	Efficacy Inferential - Placebo	Efficacy Inferential - Balovaptan 10 mg/d equivalent		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	67[12]	74[13]		
Units: Percentage of participants				
number (not applicable)				
1 - Very much improved, Week 12	1.5	0		
2 - Much improved, Week 12	16.4	20.3		
3 - Minimally improved, Week 12	38.8	25.7		
4 - No change, Week 12	40.3	54.1		
5 - Minimally worse, Week 12	3.0	0		
6 - Much worse, Week 12	0	0		
7 - Very much worse, Week 12	0	0		
1 - Very much improved, Week 24	0	2.9		
2 - Much improved, Week 24	25.8	22.1		
3 - Minimally improved, Week 24	46.8	25.0		
4 - No change, Week 24	25.8	50.0		
5 - Minimally worse, Week 24	1.6	0		
6 - Much worse, Week 24	0	0		
7 - Very much worse, Week 24	0	0		

Notes:

[12] - Week 12, n=67 Week 24, n=62

[13] - Week 12, n=74 Week 24, n=68

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Patient-Reported Pediatric Quality of Life

(PedsQL) v4.0 Generic Core Scale after 12 Weeks and 24 Weeks of Treatment for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

End point title	Change from Baseline in Patient-Reported Pediatric Quality of Life (PedsQL) v4.0 Generic Core Scale after 12 Weeks and 24 Weeks of Treatment for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

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). For children aged 8 years and above, the PedsQL 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). For children aged 5-7 years, scoring is based on a three-point scale (0=Not at all, 2=Sometimes, 4=A lot). 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:

Baseline, Weeks 12 and 24

End point values	Efficacy Inferential - Placebo	Efficacy Inferential - Balovaptan 10 mg/d equivalent		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81[14]	86[15]		
Units: Score on scale				
least squares mean (standard error)				
Change From Baseline at Week 12	2.42 (± 1.49)	6.16 (± 1.41)		
Change From Baseline at Week 24	3.70 (± 1.50)	5.98 (± 1.44)		

Notes:

[14] - Value at baseline, n=81;Change from baseline at Week 12, n=62; Change from baseline at Week 24, n=59

[15] - Value at baseline, n=86;Change from baseline at Week 12, n=72; Change from baseline at Week 24, n=65

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

Week 12

Comparison groups	Efficacy Inferential - Placebo v Efficacy Inferential - Balovaptan 10 mg/d equivalent
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Difference of Adjusted LS Means
Point estimate	3.74
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.78
upper limit	6.7

Statistical analysis title	Statistical Analysis
Statistical analysis description: Week 24	
Comparison groups	Efficacy Inferential - Placebo v Efficacy Inferential - Balovaptan 10 mg/d equivalent
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference of Adjusted LS means
Point estimate	2.28
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.73
upper limit	5.29

Secondary: Change from Baseline in Vineland-II Composite Standard Score in Adolescents and Children Independently at Weeks 12 and 24 for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

End point title	Change from Baseline in Vineland-II Composite Standard Score in Adolescents and Children Independently at Weeks 12 and 24 for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

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 caregiver in this study, during which the rater or clinician will ask to the caregiver 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:

Baseline, Weeks 12 and 24

End point values	Efficacy Inferential - Placebo	Efficacy Inferential - Balovaptan 10 mg/d equivalent		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	86		
Units: Score on scale				
arithmetic mean (standard deviation)				
5-12 Years Age, Absolute Value at Baseline	73.9 (± 9.7)	77.3 (± 10.9)		

5-12 Years Age, Change From Baseline at Week 12	3.6 (± 8.4)	1.2 (± 7.8)		
5-12 Years Age, Change From Baseline at Week 24	4.8 (± 9.1)	1.0 (± 8.4)		
13-17 Years Age, Absolute Value at Baseline	71.0 (± 10.3)	73.5 (± 8.9)		
13-17 Years Age, Change From Baseline at Week 12	1.8 (± 4.8)	3.7 (± 9.4)		
13-17 Years Age, Change From Baseline at Week 24	2.7 (± 8.6)	3.3 (± 8.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Vineland-II Adaptive Behavior Scale 2DC Score at Week 12 for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

End point title	Change From Baseline in Vineland-II Adaptive Behavior Scale 2DC Score at Week 12 for Balovaptan (R05285119) 10 mg Equivalent Compared to Placebo

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 caregiver in this study, during which the rater or clinician will ask to the caregiver 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:

Baseline, Week 12

End point values	Efficacy Inferential - Placebo	Efficacy Inferential - Balovaptan 10 mg/d equivalent		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	86		
Units: Score on scale				
least squares mean (standard error)	1.87 (± 1.00)	1.88 (± 0.97)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Efficacy Inferential - Placebo v Efficacy Inferential - Balovaptan 10 mg/d equivalent

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.992
Method	Mixed models analysis
Parameter estimate	Difference in Adjusted LS Means
Point estimate	0.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.99
upper limit	2.01

Secondary: Percentage of Participants With Adverse Events for Treatment With Balovaptan

End point title	Percentage of Participants With Adverse Events for Treatment With Balovaptan

End point description:

Treatment groups were categorized based on the tertiles of individual participant's PK exposure at Week 12. To allow clear analysis by exposure tertiles, dose adjusters were excluded from the analysis by tertiles. Dose-Adjusters were included in the "All Treated" group in the Main Study Part and Open Label Extension Part.

End point type	Secondary

End point timeframe:

Baseline to Week 24 and up to Week 76

End point values	Main Study Part, Low Exposure Tertile	Main Study Part, Medium Exposure Tertile	Main Study Part, High Exposure Tertile	Main Study Part - All Treated
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	57	66	66	196
Units: Percentage of Participants				
number (not applicable)	77.2	71.2	66.7	71.4

End point values	Open Label Extension Part, Low Exposure Tertile	Open Label Extension Part, Medium Exposure Tertile	Open Label Extension Part, High Exposure Tertile	Open Label Extension Part, All Treated
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	35	40	46	126
Units: Percentage of Participants				
number (not applicable)	68.6	70.0	78.3	72.2

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first study drug to the data cutoff date: 30 June 2020 (up to 43 months)

Adverse event reporting additional description:

Treatment groups were categorized based on the tertiles of individual participant's PK exposure at Week 12. To allow clear analysis by exposure tertiles, dose adjusters were excluded from the analysis by tertiles. Dose-Adjusters are reported as a separate group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	PK Part - Placebo

Reporting group description:

Participants in the PK Part of the study who received a matching placebo orally. Approximate treatment duration was up to 8 weeks.

Reporting group title	PK Part - Balovaptan (RO5285119) 4 mg/d equivalent

Reporting group description:

Participants in the PK Part of the study who received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 8 weeks.

Reporting group title	PK Part - Balovaptan (RO5285119) 10 mg/d equivalent

Reporting group description:

Participants in the PK Part of the study who received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 8 weeks.

Reporting group title	Main Study Part - Placebo

Reporting group description:

Participants in the Main Study Part received a matching placebo orally. Approximate treatment duration was up to 24 weeks.

Reporting group title	Main Study Part - Low Exposure Tertile

Reporting group description:

Participants in the Main Study Part in the Low Exposure Tertile received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks.

Reporting group title	Main Study Part - Medium Exposure Tertile

Reporting group description:

Participants in the Main Study Part in the Medium Exposure Tertile received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks.

Reporting group title	Main Study Part - High Exposure Tertile

Reporting group description:

Participants in the Main Study Part in the High Exposure Tertile received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks.

Reporting group title	Main Study Part - Dose-Adjusters

Reporting group description:

Participants with dose adjustment who were excluded from the analysis by tertiles. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 4 or 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 24 weeks in Main Study Part.

Reporting group title	Open Label Extension Part - Placebo

Reporting group description:

Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.

Reporting group title	Open Label Extension Part - Low Exposure Tertile

Reporting group description:

Participants in the Open Label Extension Part of the study in the Low Exposure Tertile received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks.

Reporting group title	Open Label Extension Part - Medium Exposure Tertile

Reporting group description:

Participants in the Open Label Extension Part of the study in the Medium Exposure Tertile received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.

Reporting group title	Open Label Extension Part - High Exposure Tertile

Reporting group description:

Participants in the Open Label Extension Part of the study in the High Exposure Tertile received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up 52 weeks.

Reporting group title	Open Label Extension Part - Dose-Adjusters

Reporting group description:

Participants with dose adjustment who were excluded from the analysis by tertiles. Participants received age-adjusted total daily oral dose approximately equivalent to the adult dose of 10 milligrams per day (mg/d) of balovaptan (RO5285119). Approximate treatment duration was up to 52 weeks in Open Label Extension Part.

Serious adverse events	PK Part - Placebo	PK Part - Balovaptan (RO5285119) 4 mg/d equivalent	PK Part - Balovaptan (RO5285119) 10 mg/d equivalent
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 15 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (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
Respiratory, thoracic and mediastinal disorders			
Laryngospasm			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (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
Psychiatric disorders			
Aggression			

subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (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
Agitation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (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
Anxiety			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (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
Depression			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (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
Intentional self-injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (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
Suicidal ideation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 15 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (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
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (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	Main Study Part - Placebo	Main Study Part - Low Exposure Tertile	Main Study Part - Medium Exposure Tertile
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 112 (3.57%)	1 / 57 (1.75%)	0 / 66 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (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
Respiratory, thoracic and mediastinal disorders			
Laryngospasm			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (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
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 112 (0.89%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (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
Anxiety			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (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
Depression			

subjects affected / exposed	1 / 112 (0.89%)	0 / 57 (0.00%)	0 / 66 (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
Intentional self-injury			
subjects affected / exposed	1 / 112 (0.89%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 112 (0.00%)	1 / 57 (1.75%)	0 / 66 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (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
Gastroenteritis viral			
subjects affected / exposed	1 / 112 (0.89%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (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	Main Study Part - High Exposure Tertile	Main Study Part - Dose-Adjusters	Open Label Extension Part - Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 66 (1.52%)	0 / 7 (0.00%)	2 / 68 (2.94%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			

subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (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
Respiratory, thoracic and mediastinal disorders			
Laryngospasm			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (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
Agitation			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (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
Depression			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (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
Intentional self-injury			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (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
Suicidal ideation			
subjects affected / exposed	1 / 66 (1.52%)	0 / 7 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (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	Open Label Extension Part - Low Exposure Tertile	Open Label Extension Part - Medium Exposure Tertile	Open Label Extension Part - High Exposure Tertile
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	2 / 46 (4.35%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Laryngospasm			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (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
Psychiatric disorders			
Aggression			

subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (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
Agitation			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (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
Anxiety			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (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
Intentional self-injury			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (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
Suicidal ideation			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (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
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open Label Extension Part - Dose-Adjusters		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Laryngospasm			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Agitation			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intentional self-injury			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	PK Part - Placebo	PK Part - Balovaptan (RO5285119) 4 mg/d equivalent	PK Part - Balovaptan (RO5285119) 10 mg/d equivalent
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)	7 / 11 (63.64%)	7 / 15 (46.67%)
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	1 / 12 (8.33%)	1 / 11 (9.09%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Nasal congestion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Impulsive behaviour			

subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Irritability			
subjects affected / exposed	0 / 12 (0.00%)	2 / 11 (18.18%)	0 / 15 (0.00%)
occurrences (all)	0	4	0
Mood swings			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Nightmare			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Stereotypy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Suicidal ideation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Middle insomnia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Investigations			
Weight increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Arthropod bite			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Contusion			

subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Facial bones fracture			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Poor quality sleep			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Psychomotor hyperactivity			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Neutropenia			

subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	2 / 15 (13.33%)
occurrences (all)	0	1	3
Constipation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	2 / 12 (16.67%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Mouth ulceration			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	2 / 12 (16.67%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue			

disorders			
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	1 / 12 (8.33%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Viral infection			

subjects affected / exposed	0 / 12 (0.00%)	0 / 11 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	0 / 12 (0.00%)	1 / 11 (9.09%)	0 / 15 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Main Study Part - Placebo	Main Study Part - Low Exposure Tertile	Main Study Part - Medium Exposure Tertile
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 112 (51.79%)	34 / 57 (59.65%)	31 / 66 (46.97%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	4 / 112 (3.57%)	4 / 57 (7.02%)	4 / 66 (6.06%)
occurrences (all)	4	4	4
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 112 (4.46%)	3 / 57 (5.26%)	1 / 66 (1.52%)
occurrences (all)	5	4	1
Nasal congestion			
subjects affected / exposed	5 / 112 (4.46%)	3 / 57 (5.26%)	0 / 66 (0.00%)
occurrences (all)	6	3	0
Oropharyngeal pain			
subjects affected / exposed	7 / 112 (6.25%)	2 / 57 (3.51%)	3 / 66 (4.55%)
occurrences (all)	7	2	3
Rhinorrhoea			

subjects affected / exposed	1 / 112 (0.89%)	5 / 57 (8.77%)	2 / 66 (3.03%)
occurrences (all)	1	5	2
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Impulsive behaviour			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Irritability			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Mood swings			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Nightmare			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Stereotypy			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Suicidal ideation			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Middle insomnia			
subjects affected / exposed	1 / 112 (0.89%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	1	0	0
Investigations			
Weight increased			

subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Arthropod bite			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	1 / 112 (0.89%)	2 / 57 (3.51%)	1 / 66 (1.52%)
occurrences (all)	1	2	1
Facial bones fracture			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 112 (0.89%)	3 / 57 (5.26%)	1 / 66 (1.52%)
occurrences (all)	1	4	1
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 112 (14.29%)	6 / 57 (10.53%)	7 / 66 (10.61%)
occurrences (all)	16	8	9
Poor quality sleep			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Psychomotor hyperactivity			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Syncope			

subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	5 / 112 (4.46%)	1 / 57 (1.75%)	0 / 66 (0.00%)
occurrences (all)	7	1	0
Abdominal pain upper			
subjects affected / exposed	6 / 112 (5.36%)	1 / 57 (1.75%)	2 / 66 (3.03%)
occurrences (all)	7	1	2
Constipation			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	4 / 112 (3.57%)	5 / 57 (8.77%)	4 / 66 (6.06%)
occurrences (all)	5	5	4
Mouth ulceration			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	7 / 112 (6.25%)	3 / 57 (5.26%)	2 / 66 (3.03%)
occurrences (all)	8	3	2
Vomiting			

subjects affected / exposed	6 / 112 (5.36%)	5 / 57 (8.77%)	4 / 66 (6.06%)
occurrences (all)	8	5	7
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	5 / 112 (4.46%)	1 / 57 (1.75%)	3 / 66 (4.55%)
occurrences (all)	6	1	3
Nasopharyngitis			
subjects affected / exposed	15 / 112 (13.39%)	8 / 57 (14.04%)	12 / 66 (18.18%)
occurrences (all)	15	10	17
Otitis media			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0

Rhinitis			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	1 / 66 (1.52%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	4 / 112 (3.57%)	2 / 57 (3.51%)	3 / 66 (4.55%)
occurrences (all)	5	2	3
Viral infection			
subjects affected / exposed	0 / 112 (0.00%)	3 / 57 (5.26%)	2 / 66 (3.03%)
occurrences (all)	0	3	3
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	0 / 112 (0.00%)	0 / 57 (0.00%)	0 / 66 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Main Study Part - High Exposure Tertile	Main Study Part - Dose-Adjusters	Open Label Extension Part - Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 66 (51.52%)	5 / 7 (71.43%)	35 / 68 (51.47%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	2 / 66 (3.03%)	0 / 7 (0.00%)	5 / 68 (7.35%)
occurrences (all)	2	0	5
Nasal congestion			
subjects affected / exposed	6 / 66 (9.09%)	1 / 7 (14.29%)	2 / 68 (2.94%)
occurrences (all)	7	1	2
Oropharyngeal pain			
subjects affected / exposed	4 / 66 (6.06%)	0 / 7 (0.00%)	3 / 68 (4.41%)
occurrences (all)	4	0	3
Rhinorrhoea			
subjects affected / exposed	3 / 66 (4.55%)	0 / 7 (0.00%)	1 / 68 (1.47%)
occurrences (all)	4	0	3
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	2 / 68 (2.94%)
occurrences (all)	0	0	2
Anxiety			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	5 / 68 (7.35%)
occurrences (all)	0	0	5
Impulsive behaviour			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	2 / 68 (2.94%)
occurrences (all)	0	0	2
Irritability			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Mood swings			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Nightmare			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Stereotypy			

subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Suicidal ideation			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Middle insomnia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 7 (14.29%)	0 / 68 (0.00%)
occurrences (all)	0	1	0
Investigations			
Weight increased			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	2 / 68 (2.94%)
occurrences (all)	0	0	2
Arthropod bite			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 66 (0.00%)	1 / 7 (14.29%)	0 / 68 (0.00%)
occurrences (all)	0	1	0
Facial bones fracture			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 7 (14.29%)	0 / 68 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 66 (12.12%)	0 / 7 (0.00%)	4 / 68 (5.88%)
occurrences (all)	15	0	5
Poor quality sleep			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0

Psychomotor hyperactivity			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	6 / 66 (9.09%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	8	0	0
Abdominal pain upper			
subjects affected / exposed	4 / 66 (6.06%)	0 / 7 (0.00%)	3 / 68 (4.41%)
occurrences (all)	15	0	3
Constipation			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			

subjects affected / exposed	7 / 66 (10.61%)	0 / 7 (0.00%)	3 / 68 (4.41%)
occurrences (all)	8	0	5
Mouth ulceration			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	4 / 66 (6.06%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	4	0	0
Vomiting			
subjects affected / exposed	4 / 66 (6.06%)	0 / 7 (0.00%)	2 / 68 (2.94%)
occurrences (all)	4	0	2
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	1 / 68 (1.47%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	4 / 68 (5.88%)
occurrences (all)	0	0	4
Gastroenteritis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	3 / 66 (4.55%)	1 / 7 (14.29%)	4 / 68 (5.88%)
occurrences (all)	3	1	4

Nasopharyngitis			
subjects affected / exposed	11 / 66 (16.67%)	2 / 7 (28.57%)	9 / 68 (13.24%)
occurrences (all)	12	2	11
Otitis media			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	2 / 68 (2.94%)
occurrences (all)	0	0	2
Rhinitis			
subjects affected / exposed	1 / 66 (1.52%)	1 / 7 (14.29%)	0 / 68 (0.00%)
occurrences (all)	2	1	0
Sinusitis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	3 / 68 (4.41%)
occurrences (all)	0	0	3
Upper respiratory tract infection			
subjects affected / exposed	5 / 66 (7.58%)	0 / 7 (0.00%)	3 / 68 (4.41%)
occurrences (all)	7	0	4
Viral infection			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	0 / 66 (0.00%)	0 / 7 (0.00%)	0 / 68 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Open Label Extension Part - Low Exposure Tertile	Open Label Extension Part - Medium Exposure Tertile	Open Label Extension Part - High Exposure Tertile
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 35 (60.00%)	25 / 40 (62.50%)	27 / 46 (58.70%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Pyrexia			

subjects affected / exposed	3 / 35 (8.57%)	2 / 40 (5.00%)	3 / 46 (6.52%)
occurrences (all)	3	3	3
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 35 (0.00%)	1 / 40 (2.50%)	4 / 46 (8.70%)
occurrences (all)	0	1	4
Nasal congestion			
subjects affected / exposed	2 / 35 (5.71%)	3 / 40 (7.50%)	1 / 46 (2.17%)
occurrences (all)	2	3	1
Oropharyngeal pain			
subjects affected / exposed	1 / 35 (2.86%)	2 / 40 (5.00%)	4 / 46 (8.70%)
occurrences (all)	2	2	4
Rhinorrhoea			
subjects affected / exposed	3 / 35 (8.57%)	1 / 40 (2.50%)	3 / 46 (6.52%)
occurrences (all)	3	1	4
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 35 (2.86%)	2 / 40 (5.00%)	1 / 46 (2.17%)
occurrences (all)	1	2	1
Anxiety			
subjects affected / exposed	2 / 35 (5.71%)	4 / 40 (10.00%)	1 / 46 (2.17%)
occurrences (all)	2	4	1
Impulsive behaviour			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0

Irritability			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Mood swings			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Nightmare			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Stereotypy			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Suicidal ideation			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Middle insomnia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Investigations			
Weight increased			
subjects affected / exposed	2 / 35 (5.71%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	2 / 35 (5.71%)	2 / 40 (5.00%)	2 / 46 (4.35%)
occurrences (all)	2	2	3
Arthropod bite			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Facial bones fracture			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			

Tachycardia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 35 (8.57%)	2 / 40 (5.00%)	5 / 46 (10.87%)
occurrences (all)	4	2	7
Poor quality sleep			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Psychomotor hyperactivity			
subjects affected / exposed	1 / 35 (2.86%)	0 / 40 (0.00%)	1 / 46 (2.17%)
occurrences (all)	1	0	1
Seizure			
subjects affected / exposed	0 / 35 (0.00%)	2 / 40 (5.00%)	0 / 46 (0.00%)
occurrences (all)	0	2	0
Somnolence			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	2	0	0
Neutropenia			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Abdominal discomfort			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	2 / 35 (5.71%)	0 / 40 (0.00%)	2 / 46 (4.35%)
occurrences (all)	2	0	2
Constipation			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	2 / 35 (5.71%)	1 / 40 (2.50%)	2 / 46 (4.35%)
occurrences (all)	2	1	3
Mouth ulceration			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	2 / 35 (5.71%)	1 / 40 (2.50%)	3 / 46 (6.52%)
occurrences (all)	4	1	3
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 35 (0.00%)	2 / 40 (5.00%)	0 / 46 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Bronchitis			

subjects affected / exposed	0 / 35 (0.00%)	2 / 40 (5.00%)	0 / 46 (0.00%)
occurrences (all)	0	2	0
Ear infection			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Gastroenteritis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	3 / 35 (8.57%)	0 / 40 (0.00%)	2 / 46 (4.35%)
occurrences (all)	3	0	2
Nasopharyngitis			
subjects affected / exposed	5 / 35 (14.29%)	10 / 40 (25.00%)	6 / 46 (13.04%)
occurrences (all)	5	14	7
Otitis media			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 35 (0.00%)	1 / 40 (2.50%)	1 / 46 (2.17%)
occurrences (all)	0	1	2
Rhinitis			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 35 (0.00%)	3 / 40 (7.50%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Upper respiratory tract infection			
subjects affected / exposed	4 / 35 (11.43%)	3 / 40 (7.50%)	3 / 46 (6.52%)
occurrences (all)	6	3	3
Viral infection			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	0 / 35 (0.00%)	0 / 40 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Open Label Extension Part - Dose-Adjusters		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Nasal congestion			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		

Anxiety subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Impulsive behaviour subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Insomnia subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2		
Irritability subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Mood swings subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Nightmare subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Stereotypy subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Suicidal ideation subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Middle insomnia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Investigations Weight increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Injury, poisoning and procedural complications Accidental overdose subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Arthropod bite			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Contusion			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Facial bones fracture			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Poor quality sleep			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Psychomotor hyperactivity			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Seizure			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0		
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0		
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Mouth ulceration subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0		
Renal and urinary disorders			

Pollakiuria			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Ear infection			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Otitis media			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Pharyngitis streptococcal			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			

subjects affected / exposed occurrences (all) Viral infection subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0 0 / 5 (0.00%) 0		
Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 August 2016	Protocol was amended to include age range change to 13-17 years for adolescents and 5-12 years for children. The PK schedule was revised so that the visit with the most intense PK sampling was moved from Week 1 to Week 2. This was to ensure that PK assessments were taken within the first cohorts of 24 adolescents and 24 children at steady state for all major metabolites.
30 January 2017	Protocol was amended to include participants who were obliged to stop dosing on or before Week 8, due to lack of sufficient data to inform IMC/ SOC decision on final dose, were allowed to re-start in the main study.
19 May 2017	Protocol was amended to include a change in the exclusion criterion for body mass index (BMI). BMI at or above the 95th percentile for the same age and sex was considered to be safe. The 99th percentile was used instead.
29 March 2018	Protocol was amended to include updated text to specify that the primary endpoint will be assessed based on the change from baseline on the Vineland™-II Adaptive Behavior Scales, second edition (Vineland™-II) Two Domain Composite (2DC) instead of Vineland™-II Adaptive Behavior Scales, second edition (Vineland™-II) Composite standard score. The following secondary objectives were added: Proportion of participants with >=6-point improvement in the Vineland™-II 2DC score to evaluate clinically meaningful response; Patient-reported Pediatric Quality of Life (PedsQL) v4.0 Generic Core Scale after 12 weeks and 24 weeks of treatment; Evaluate safety and tolerability of up to 76 weeks of treatment with balovaptan. The secondary objective was changed from "Change from baseline on the Vineland™-II Composite standard score after 12 weeks and 24 weeks of treatment" to "Change from baseline on the Vineland™-II 2DC score after 12 weeks and 24 weeks of treatment". An Open Label Extension was added. The total duration of the study was updated from 39 weeks to 91 weeks and the end of study was updated from 31 weeks to 83 weeks.
19 December 2018	Protocol was amended to include study design change to a single dose (10 mg equivalent balovaptan) compared with Placebo in accordance to a randomization ratio of 1:1 of balovaptan 10 mg equivalent: Placebo. Adolescent participants who had been discontinued because of lack of dose confirmation (per protocol prior to Week 8) were to be replaced in the study. The total sample size of the study was increased to 340 participants. The initial starting dose (main study) was changed following review of available safety and PK data from the study. A table was added to outline updated starting doses for adolescents and children, aged 8 to 17 years.

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.

Limited data collected in OLE part because study was terminated early after primary analysis.

Notes: