



Clinical trial results:

A 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age with Short Bowel Syndrome who are Dependent on Parenteral Support

Summary

EudraCT number	2015-002252-27
Trial protocol	GB IT FI BE
Global end of trial date	18 August 2017

Results information

Result version number	v1 (current)
This version publication date	04 March 2018
First version publication date	04 March 2018

Trial information

Trial identification

Sponsor protocol code	TED-C14-006
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02682381
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	300 Shire Way, Lexington, MA, United States, 02421
Public contact	Study Physician, Shire, 1 866-842-5335,
Scientific contact	Study Physician, Shire, 1 866-842-5335,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000482-PIP01-08
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	18 August 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the safety, pharmacokinetics (PK), and efficacy/pharmacodynamics (PD) of teduglutide in pediatric subjects through 17 years of age with short bowel syndrome (SBS) and who are dependent on parenteral support.

Protection of trial subjects:

This study was conducted in accordance with current applicable regulations, International Council for Harmonisation (ICH) of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	United States: 39
Worldwide total number of subjects	59
EEA total number of subjects	15

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)	1

Children (2-11 years)	53
Adolescents (12-17 years)	5
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 27 study centers in the United States, Belgium, Canada, the United Kingdom, Finland, Germany and Italy between 03 June 2016 (first subject first visit) and 18 August 2017 (last subject last visit).

Pre-assignment

Screening details:

Overall, 59 subjects were enrolled; 50 in the teduglutide treatment arm (24 subjects in the 0.025 milligram per kilogram per day (mg/kg/day) dose group and 26 subjects in the 0.05 mg/kg/day dose group) and 9 in the standard of care arm.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	0.025 mg/kg/day Teduglutide

Arm description:

Subjects received 0.025 mg/kg/day of teduglutide subcutaneously for 24 weeks along with standard medical therapy.

Arm type	Experimental
Investigational medicinal product name	Teduglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received teduglutide subcutaneously for 24 weeks along with standard medical therapy.

Arm title	0.05 mg/kg/day Teduglutide
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Arm description:

Subjects received 0.05 mg/kg/day of teduglutide subcutaneously for 24 weeks along with standard medical therapy.

Arm type	Experimental
Investigational medicinal product name	Teduglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received teduglutide subcutaneously for 24 weeks along with standard medical therapy.

Arm title	Standard of care
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Arm description:

Subjects received standard medical therapy.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care
Started	24	26	9
Completed	24	26	9

Baseline characteristics

Reporting groups

Reporting group title	0.025 mg/kg/day Teduglutide
Reporting group description: Subjects received 0.025 mg/kg/day of teduglutide subcutaneously for 24 weeks along with standard medical therapy.	
Reporting group title	0.05 mg/kg/day Teduglutide
Reporting group description: Subjects received 0.05 mg/kg/day of teduglutide subcutaneously for 24 weeks along with standard medical therapy.	
Reporting group title	Standard of care
Reporting group description: Subjects received standard medical therapy.	

Reporting group values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care
Number of subjects	24	26	9
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	6.6 ± 3.61	6.2 ± 3.67	5.7 ± 4.72
Gender categorical Units: Subjects			
Female	8	7	3
Male	16	19	6
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	5	4
Not Hispanic or Latino	16	20	2
Unknown or Not Reported	3	1	3
Race Units: Subjects			
White	16	21	2
Black or African American	3	3	1
Asian	1	1	1
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1	0	2
Not allowed based on local regulations	3	1	3

Reporting group values	Total		
Number of subjects	59		

Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	18		
Male	41		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	14		
Not Hispanic or Latino	38		
Unknown or Not Reported	7		
Race			
Units: Subjects			
White	39		
Black or African American	7		
Asian	3		
American Indian or Alaska Native	0		
Native Hawaiian or Other Pacific Islander	0		
Other	3		
Not allowed based on local regulations	7		

End points

End points reporting groups

Reporting group title	0.025 mg/kg/day Teduglutide
Reporting group description: Subjects received 0.025 mg/kg/day of teduglutide subcutaneously for 24 weeks along with standard medical therapy.	
Reporting group title	0.05 mg/kg/day Teduglutide
Reporting group description: Subjects received 0.05 mg/kg/day of teduglutide subcutaneously for 24 weeks along with standard medical therapy.	
Reporting group title	Standard of care
Reporting group description: Subjects received standard medical therapy.	

Primary: Number of Subjects who Achieved at Least a 20 Percent (%) Reduction in Weight-Normalized Average Daily Parenteral Nutrition Intravenous (PN/IV) Volume at Week 24

End point title	Number of Subjects who Achieved at Least a 20 Percent (%) Reduction in Weight-Normalized Average Daily Parenteral Nutrition Intravenous (PN/IV) Volume at Week 24 ^[1]
End point description: Reduction in weight-normalized PN/IV volume was performed using both subject diary and investigator prescribed data. Number of subjects who achieved at least a 20% reduction in weight-normalized PN/IV volume between the baseline and week 24/end of treatment (EOT) visit were reported. Intention to treat (ITT) population included all enrolled subjects.	
End point type	Primary
End point timeframe: Week 24	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: Subject				
Subject Diary	13	18	1	
Investigator Prescribed	13	18	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events
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End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that did not necessarily have a causal relationship with this treatment. TEAEs were defined as AEs that started or worsened on or after the date of first dose for treatment groups and those that started or worsened on or after the baseline visit for standard of care group. Safety analysis population included all subjects who received at least 1 dose of teduglutide and had undergone at least 1 post-baseline safety assessment in teduglutide treatment group or subjects who had undergone at least 1 post-baseline safety assessment in standard of care treatment group.

End point type	Secondary
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End point timeframe:

From start of study treatment up to 28 weeks
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End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: Subject				
Subject	24	25	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Were Completely Weaned off Parenteral Nutrition Intravenous (PN/IV) Support at Week 24

End point title	Number of Subjects Who Were Completely Weaned off Parenteral Nutrition Intravenous (PN/IV) Support at Week 24
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End point description:

A subject was considered to have achieved independence from PN/IV support (completely weaned off PN/IV) if the investigator prescribed no PN/IV at EOT and there was no use of PN/IV recorded in the subject diary during the week prior to EOT. ITT population included all enrolled subjects.

End point type	Secondary
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End point timeframe:

Week 24

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: Subject				
Subject	2	3	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Parenteral Nutrition Intravenous (PN/IV) Volume at Week 24

End point title	Change From Baseline in Parenteral Nutrition Intravenous (PN/IV) Volume at Week 24
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End point description:

Change in PN/IV volume was reported based on the subject diary and the investigator prescribed data. ITT population included all enrolled subjects. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: Milliliter per kilogram per day				
arithmetic mean (standard deviation)				
Subject Diary (n=20,25,9)	-16.16 (± 10.52)	-23.30 (± 17.50)	-6.03 (± 4.55)	
Investigator Prescribed (n=24,26,9)	-11.28 (± 15.51)	-22.13 (± 17.92)	-5.84 (± 9.80)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Parenteral Nutrition Intravenous (PN/IV) Calories at Week 24

End point title	Change From Baseline in Parenteral Nutrition Intravenous (PN/IV) Calories at Week 24
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End point description:

Change in PN/IV calories was reported based on the subject diary and the investigator prescribed data. ITT population included all enrolled subjects. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: Kilocalorie per kilogram per day				
arithmetic mean (standard deviation)				
Subject Diary (n=20,25,9)	-14.92 (± 8.29)	-18.99 (± 14.28)	-0.46 (± 4.95)	
Investigator Prescribed (n=24,25,9)	-11.76 (± 10.46)	-18.51 (± 13.22)	-0.27 (± 2.73)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plasma Citrulline Levels at Week 24

End point title	Change From Baseline in Plasma Citrulline Levels at Week 24
End point description:	Plasma citrulline levels was assessed. ITT population included all enrolled subjects.
End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: Micromole per liter (mcmol/L)				
arithmetic mean (standard deviation)				
Change at baseline (n=21,24,8)	7.7 (± 8.50)	12.0 (± 12.0)	0.1 (± 7.79)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Enteral Nutritional Volume at Week 24

End point title	Change From Baseline in Enteral Nutritional Volume at Week 24
End point description:	Enteral nutrition was defined as specialized formula taken orally or by tube feeding, and excluded tube

foods and other fluids. Enteral Nutritional Volume was assessed. ITT population included all enrolled subjects. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively.

End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: Milliliter per kilogram per day				
arithmetic mean (standard deviation)				
Subject Diary (n=18,25,9)	7.69 (± 13.46)	10.96 (± 16.59)	0.74 (± 5.91)	
Investigator Prescribed (n=18,21,5)	7.67 (± 17.77)	8.17 (± 17.87)	0.33 (± 0.90)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Enteral Nutritional Calories at Week 24

End point title	Change From Baseline in Enteral Nutritional Calories at Week 24
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End point description:

Enteral nutrition was defined as specialized formula taken orally or by tube feeding, and excluded table foods and other fluids. Enteral Nutritional Calories was assessed. ITT population included all enrolled subjects. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively.

End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: Kilocalorie per kilogram per day				
arithmetic mean (standard deviation)				
Subject Diary (n=18,25,9)	8.43 (± 14.39)	12.98 (± 18.93)	4.22 (± 13.75)	
Investigator Prescribed (n=18,21,5)	7.29 (± 15.88)	11.47 (± 21.13)	6.66 (± 14.77)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 24 in Parenteral Nutrition Intravenous (PN/IV) Volume at Week 28

End point title	Change From Week 24 in Parenteral Nutrition Intravenous (PN/IV) Volume at Week 28
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End point description:

Parenteral nutrition intravenous (PN/IV) volume was assessed. ITT population included all enrolled subjects. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively.

End point type	Secondary
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End point timeframe:

Week 24, Week 28

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: Milliliter per kilogram per day				
arithmetic mean (standard deviation)				
Subject Diary (n=24,26,8)	2.63 (± 7.80)	1.52 (± 12.68)	-2.99 (± 4.94)	
Investigator Prescribed (n=24,26,9)	2.13 (± 6.95)	-0.35 (± 5.96)	-0.91 (± 2.18)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 24 in Parenteral Nutrition Intravenous (PN/IV) Calories at Week 28

End point title	Change From Week 24 in Parenteral Nutrition Intravenous (PN/IV) Calories at Week 28
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End point description:

Parenteral Nutrition Intravenous (PN/IV) Calories was assessed. ITT population included all enrolled subjects. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively.

End point type	Secondary
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End point timeframe:

Week 24, Week 28

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: Kilocalorie per kilogram per day				
arithmetic mean (standard deviation)				
Subject Diary (n=24,26,8)	0.88 (± 2.94)	-0.91 (± 7.14)	-4.21 (± 10.30)	
Investigator Prescribed (n=24,26,9)	0.55 (± 3.42)	0.08 (± 6.13)	-4.34 (± 11.22)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 24 in Plasma Citrulline Levels at Week 28

End point title	Change From Week 24 in Plasma Citrulline Levels at Week 28
End point description:	Plasma Citrulline Levels was assessed. ITT population included all enrolled subjects.
End point type	Secondary
End point timeframe:	Week 24, Week 28

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: mcmol/L				
arithmetic mean (standard deviation)				
Change at Week 28 (n=24,25,9)	-6.0 (± 9.26)	-9.5 (± 10.33)	1.8 (± 6.48)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 24 in Enteral Nutritional Volume at Week 28

End point title	Change From Week 24 in Enteral Nutritional Volume at Week 28
End point description:	Enteral nutrition was defined as specialized formula taken orally or by tube feeding, and excluded tube

foods and other fluids. Enteral Nutritional Volume was assessed. ITT population included all enrolled subjects. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively.

End point type	Secondary
End point timeframe:	
Week 24, Week 28	

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: Milliliter per kilogram per day				
arithmetic mean (standard deviation)				
Subject Diary (n=23,26,8)	-0.68 (± 3.86)	1.38 (± 8.41)	-0.75 (± 6.78)	
Investigator Prescribed (n=18,22,5)	1.67 (± 5.73)	0.68 (± 6.65)	0.39 (± 0.57)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 24 in Enteral Nutritional Calories at Week 28

End point title	Change From Week 24 in Enteral Nutritional Calories at Week 28
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End point description:

Enteral nutrition was defined as specialized formula taken orally or by tube feeding, and excluded table foods and other fluids. Enteral Nutritional Calories was assessed. ITT population included all enrolled subjects. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively.

End point type	Secondary
End point timeframe:	
Week 24, Week 28	

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: Kilocalorie per kilogram per day				
arithmetic mean (standard deviation)				
Subject Diary (n=23,26,8)	-1.07 (± 4.36)	-0.14 (± 7.73)	-0.42 (± 6.13)	
Investigator Prescribed (n=18,22,5)	1.28 (± 4.30)	-0.11 (± 3.77)	0.45 (± 0.64)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Weight Z-score at Week 28

End point title	Change From Baseline in Body Weight Z-score at Week 28
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End point description:

Z-score was calculated as (observed value - median value of the reference population) / standard deviation value of reference population. Centers for Disease Control and Prevention (age greater than or equal to \geq 2 years old) and World Health Organization (age less than $<$ 2 years old) Z-score calculation charts were used for calculation. Safety analysis population included all subjects who received at least 1 dose of teduglutide and had undergone at least 1 post-baseline safety assessment in teduglutide treatment group or subjects who had undergone at least 1 post-baseline safety assessment in standard of care treatment group.

End point type	Secondary
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End point timeframe:

Baseline, Week 28

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: Z-score				
arithmetic mean (standard deviation)				
Z-score	-0.12 (\pm 0.41)	-0.18 (\pm 0.59)	0.05 (\pm 0.37)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Height Z-score at Week 28

End point title	Change From Baseline in Body Height Z-score at Week 28
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End point description:

Z-score was calculated as (observed value - median value of the reference population) / standard deviation value of reference population. Centers for Disease Control and Prevention \geq 2 years old) and World Health Organization (age $<$ 2 years old) Z-score calculation charts were used for calculation. Safety analysis population included all subjects who received at least 1 dose of teduglutide and had undergone at least 1 post-baseline safety assessment in teduglutide treatment group or subjects who had undergone at least 1 post-baseline safety assessment in standard of care treatment group.

End point type	Secondary
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End point timeframe:

Baseline, Week 28

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	25	9	
Units: Z-score				
arithmetic mean (standard deviation)				
Z-score	0 (± 0.29)	0.05 (± 0.45)	0.16 (± 0.66)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Head Circumference Z-score at Week 28

End point title	Change From Baseline in Head Circumference Z-score at Week 28
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End point description:

Head circumference was collected only for subjects of less than or equal to (\leq) 36 months of age at the time of measurement. Z-score was calculated as (observed value - median value of the reference population) / standard deviation value of reference population. Centers for Disease Control and Prevention \geq 2 years old) and World Health Organization (age < 2 years old) Z-score calculation charts were used for calculation. Safety analysis population included all subjects who received at least 1 dose of teduglutide and had undergone at least 1 post-baseline safety assessment in teduglutide treatment group or subjects who had undergone at least 1 post-baseline safety assessment in standard of care treatment group. In the below table, "99999" signifies that the standard deviation was not calculated due to less number of subjects.

End point type	Secondary
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End point timeframe:

Baseline, Week 28

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[2]	0 ^[3]	1	
Units: Z-score				
arithmetic mean (standard deviation)				
Z-score	()	()	-0.014 (± 99999)	

Notes:

[2] - Head circumference was planned to be collected only for subjects \leq 36 months of age.

[3] - Head circumference was planned to be collected only for subjects \leq 36 months of age.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Mass Index (BMI) Z-score at Week 28

End point title	Change From Baseline in Body Mass Index (BMI) Z-score at Week 28
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End point description:

Z-score was calculated as (observed value - median value of the reference population) / standard deviation value of reference population. Centers for Disease Control and Prevention ≥ 2 years old) and World Health Organization (age < 2 years old) Z-score calculation charts were used for calculation. Safety analysis population included all subjects who received at least 1 dose of teduglutide and had undergone at least 1 post-baseline safety assessment in teduglutide treatment group or subjects who had undergone at least 1 post-baseline safety assessment in standard of care treatment group.

End point type	Secondary
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End point timeframe:

Baseline, Week 28

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: Z-score				
arithmetic mean (standard deviation)				
Z-score (n=24,25,9)	-0.13 (\pm 0.57)	-0.22 (\pm 0.70)	-0.25 (\pm 1.42)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From baseline in Subjects' Stool Consistency at Week 28

End point title	Change From baseline in Subjects' Stool Consistency at Week 28
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End point description:

Stool consistency was assessed by typical stool form based on Bristol Stool Form Scale: 1 - Separate hard lumps, hard to pass, 2 - Sausage-shaped, but lumpy, 3 - Like a sausage but with cracks on the surface, 4 - Like a sausage or snake, smooth and soft, 5 - Soft blobs with clear-cut edges, 6 - Fluffy pieces with ragged edges, a mushy stool, 7 - Watery, no solid pieces, entirely liquid. Safety analysis population included all subjects who received at least 1 dose of teduglutide and had undergone at least 1 post-baseline safety assessment in teduglutide treatment group or subjects who had undergone at least 1 post-baseline safety assessment in standard of care treatment group.

End point type	Secondary
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End point timeframe:

Baseline, Week 28

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: Average Bristol Stool Form Score				
arithmetic mean (standard deviation)				
Change at baseline (n=8,16,2)	-1.3 (\pm 1.77)	-1.4 (\pm 1.38)	-3.3 (\pm 0.35)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hours Per Day of Parenteral Nutrition Intravenous (PN/IV) Support

End point title	Change From Baseline in Hours Per Day of Parenteral Nutrition Intravenous (PN/IV) Support
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End point description:

The mean duration of the PN/IV infusions in hours, on the days when PN/IV was administered was assessed. ITT population included all enrolled subjects. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively.

End point type	Secondary
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End point timeframe:

Baseline, week 24

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: Hours per day (hours/day)				
arithmetic mean (standard deviation)				
Subject Diary (n=22,26,9)	-2.47 (± 2.73)	-3.03 (± 3.84)	-0.21 (± 0.69)	
Investigator Prescribed (n=24,26,9)	-1.48 (± 3.59)	-1.79 (± 3.52)	0.11 (± 0.33)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Days Per Week of Parenteral Nutrition Intravenous (PN/IV) Support at Week 24

End point title	Change From Baseline in Days Per Week of Parenteral Nutrition Intravenous (PN/IV) Support at Week 24
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End point description:

The number of days per week of PN/IV infusions was assessed. ITT population included all enrolled subjects. In the below table, "n" signifies subjects who were evaluable for the specified category, respectively.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	26	9	
Units: Days per week (Days/week)				
arithmetic mean (standard deviation)				
Subject Diary (n=22,26,9)	-0.88 (± 1.78)	-1.34 (± 2.24)	0.0 (± 0.0)	
Investigator Prescribed (n=24,26,9)	-0.79 (± 1.62)	-1.42 (± 2.32)	0 (± 0)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment up to 28 weeks

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	0.025 mg/kg/day Teduglutide
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Reporting group description:

Subjects received 0.025 mg/kg/day of teduglutide subcutaneously for 24 weeks along with standard medical therapy.

Reporting group title	0.05 mg/kg/day Teduglutide
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Reporting group description:

Subjects received 0.05 mg/kg/day of teduglutide subcutaneously for 24 weeks along with standard medical therapy.

Reporting group title	Standard of care
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Reporting group description:

Subjects received standard medical therapy.

Serious adverse events	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 24 (62.50%)	20 / 26 (76.92%)	4 / 9 (44.44%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood urea increased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	0 / 9 (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
Transaminases increased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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
Vascular disorders			
Superior vena cava syndrome			

subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 24 (16.67%)	7 / 26 (26.92%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 6	0 / 8	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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
Faecaloma			
subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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
Ileus			
subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	0 / 9 (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
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	0 / 9 (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

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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
Hypocapnia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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			
Bacteraemia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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
Catheter site infection			
subjects affected / exposed	0 / 24 (0.00%)	3 / 26 (11.54%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corona virus infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 24 (4.17%)	3 / 26 (11.54%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	0 / 9 (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
Fungaemia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastritis viral			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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
Influenza			
subjects affected / exposed	2 / 24 (8.33%)	2 / 26 (7.69%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metapneumovirus infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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
Orchitis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	0 / 9 (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
Otitis media			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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
Otitis media acute			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	0 / 9 (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
Pneumonia			

subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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
Roseola			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotavirus infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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
Subcutaneous abscess			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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
Upper respiratory tract infection			
subjects affected / exposed	2 / 24 (8.33%)	2 / 26 (7.69%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 24 (0.00%)	2 / 26 (7.69%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device breakage	Additional description: TEAEs coded to Product issues were related to central line complications, and not due to complications of the investigational product and ancillary supplies.		
subjects affected / exposed	2 / 24 (8.33%)	2 / 26 (7.69%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation	Additional description: TEAEs coded to Product issues were related to central line complications, and not due to complications of the investigational product and ancillary supplies.		
subjects affected / exposed	1 / 24 (4.17%)	0 / 26 (0.00%)	0 / 9 (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
Device issue	Additional description: TEAEs coded to Product issues were related to central line complications, and not due to complications of the investigational product and ancillary supplies.		
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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
Device occlusion	Additional description: TEAEs coded to Product issues were related to central line complications, and not due to complications of the investigational product and ancillary supplies.		
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	0 / 9 (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
Dehydration			
subjects affected / exposed	4 / 24 (16.67%)	0 / 26 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			

subjects affected / exposed	1 / 24 (4.17%)	1 / 26 (3.85%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	1 / 24 (4.17%)	1 / 26 (3.85%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Standard of care
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 24 (100.00%)	23 / 26 (88.46%)	9 / 9 (100.00%)
General disorders and administration site conditions			
Catheter site erythema			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	2 / 9 (22.22%)
occurrences (all)	0	1	2
Catheter site related reaction			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Injection site bruising			
subjects affected / exposed	3 / 24 (12.50%)	1 / 26 (3.85%)	0 / 9 (0.00%)
occurrences (all)	4	1	0
Medical device site pain			
subjects affected / exposed	0 / 24 (0.00%)	2 / 26 (7.69%)	1 / 9 (11.11%)
occurrences (all)	0	2	1
Pain			
subjects affected / exposed	2 / 24 (8.33%)	1 / 26 (3.85%)	0 / 9 (0.00%)
occurrences (all)	2	1	0
Pyrexia			
subjects affected / exposed	5 / 24 (20.83%)	6 / 26 (23.08%)	3 / 9 (33.33%)
occurrences (all)	6	9	4
Immune system disorders			

Seasonal allergy subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	2 / 26 (7.69%) 2	0 / 9 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	10 / 26 (38.46%) 11	3 / 9 (33.33%) 4
Hyperventilation subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 26 (0.00%) 0	1 / 9 (11.11%) 1
Nasal congestion subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	1 / 26 (3.85%) 1	1 / 9 (11.11%) 2
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 26 (3.85%) 1	1 / 9 (11.11%) 1
Rhinorrhoea subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3	0 / 26 (0.00%) 0	1 / 9 (11.11%) 1
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 26 (0.00%) 0	1 / 9 (11.11%) 1
Product issues			
Device breakage subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	2 / 26 (7.69%) 2	0 / 9 (0.00%) 0
Device occlusion subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3	0 / 26 (0.00%) 0	0 / 9 (0.00%) 0
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	7 / 24 (29.17%) 7	2 / 26 (7.69%) 2	0 / 9 (0.00%) 0
Aspartate aminotransferase increased			

subjects affected / exposed occurrences (all)	5 / 24 (20.83%) 5	0 / 26 (0.00%) 0	0 / 9 (0.00%) 0
Blood bicarbonate decreased subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 5	0 / 26 (0.00%) 0	0 / 9 (0.00%) 0
Blood triglycerides increased subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	1 / 26 (3.85%) 1	0 / 9 (0.00%) 0
Gamma-Glutamyltransferase increased subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 26 (0.00%) 0	0 / 9 (0.00%) 0
Lymph node palpable subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 26 (0.00%) 0	1 / 9 (11.11%) 1
Transaminases increased subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 26 (0.00%) 0	1 / 9 (11.11%) 1
Injury, poisoning and procedural complications Anaesthetic complication neurological subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 26 (0.00%) 0	1 / 9 (11.11%) 1
Stoma site erythema subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 26 (7.69%) 3	0 / 9 (0.00%) 0
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 26 (0.00%) 0	1 / 9 (11.11%) 2
Headache subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 4	5 / 26 (19.23%) 7	1 / 9 (11.11%) 3
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 26 (3.85%) 1	1 / 9 (11.11%) 1

Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 24 (4.17%)	1 / 26 (3.85%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 24 (0.00%)	2 / 26 (7.69%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Abdominal pain			
subjects affected / exposed	4 / 24 (16.67%)	6 / 26 (23.08%)	0 / 9 (0.00%)
occurrences (all)	5	7	0
Abdominal pain lower			
subjects affected / exposed	2 / 24 (8.33%)	0 / 26 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Abdominal pain upper			
subjects affected / exposed	3 / 24 (12.50%)	3 / 26 (11.54%)	1 / 9 (11.11%)
occurrences (all)	8	3	1
Diarrhoea			
subjects affected / exposed	8 / 24 (33.33%)	2 / 26 (7.69%)	1 / 9 (11.11%)
occurrences (all)	9	3	1
Nausea			
subjects affected / exposed	3 / 24 (12.50%)	3 / 26 (11.54%)	1 / 9 (11.11%)
occurrences (all)	3	3	1
Perianal erythema			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	1 / 9 (11.11%)
occurrences (all)	0	1	2
Proctalgia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 26 (3.85%)	1 / 9 (11.11%)
occurrences (all)	0	1	2
Vomiting			
subjects affected / exposed	10 / 24 (41.67%)	8 / 26 (30.77%)	5 / 9 (55.56%)
occurrences (all)	23	17	7
Hepatobiliary disorders			
Drug-Induced liver injury			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			

Dermatitis diaper subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 20	0 / 26 (0.00%) 0	0 / 9 (0.00%) 0
Eczema subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	1 / 26 (3.85%) 1	1 / 9 (11.11%) 1
Excessive granulation tissue subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 26 (3.85%) 1	1 / 9 (11.11%) 1
Rash subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	1 / 26 (3.85%) 4	1 / 9 (11.11%) 1
Red man syndrome subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 26 (0.00%) 0	1 / 9 (11.11%) 1
Renal and urinary disorders Nephrolithiasis subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 26 (3.85%) 1	1 / 9 (11.11%) 1
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 26 (0.00%) 0	1 / 9 (11.11%) 1
Pain in extremity subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 26 (0.00%) 0	0 / 9 (0.00%) 0
Infections and infestations Cellulitis subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3	0 / 26 (0.00%) 0	0 / 9 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3	1 / 26 (3.85%) 1	0 / 9 (0.00%) 0
Device related infection subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 26 (7.69%) 2	0 / 9 (0.00%) 0

Ear infection			
subjects affected / exposed	1 / 24 (4.17%)	3 / 26 (11.54%)	1 / 9 (11.11%)
occurrences (all)	1	3	1
Gastroenteritis viral			
subjects affected / exposed	3 / 24 (12.50%)	0 / 26 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal bacterial overgrowth			
subjects affected / exposed	2 / 24 (8.33%)	0 / 26 (0.00%)	0 / 9 (0.00%)
occurrences (all)	6	0	0
Nasopharyngitis			
subjects affected / exposed	4 / 24 (16.67%)	6 / 26 (23.08%)	2 / 9 (22.22%)
occurrences (all)	4	9	2
Otitis media			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 24 (0.00%)	2 / 26 (7.69%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Respiratory tract infection			
subjects affected / exposed	0 / 24 (0.00%)	2 / 26 (7.69%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Rhinitis			
subjects affected / exposed	1 / 24 (4.17%)	5 / 26 (19.23%)	0 / 9 (0.00%)
occurrences (all)	1	6	0
Upper respiratory tract infection			
subjects affected / exposed	5 / 24 (20.83%)	6 / 26 (23.08%)	4 / 9 (44.44%)
occurrences (all)	7	8	5
Urinary tract infection			
subjects affected / exposed	2 / 24 (8.33%)	1 / 26 (3.85%)	0 / 9 (0.00%)
occurrences (all)	4	1	0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1

Viral infection			
subjects affected / exposed	3 / 24 (12.50%)	1 / 26 (3.85%)	1 / 9 (11.11%)
occurrences (all)	4	2	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 26 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	2 / 24 (8.33%)	0 / 26 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Dehydration			
subjects affected / exposed	5 / 24 (20.83%)	1 / 26 (3.85%)	0 / 9 (0.00%)
occurrences (all)	9	1	0
Metabolic acidosis			
subjects affected / exposed	2 / 24 (8.33%)	0 / 26 (0.00%)	0 / 9 (0.00%)
occurrences (all)	4	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2015	<ul style="list-style-type: none">- Plasma citrulline to be collected from all study subjects, regardless of treatment group.- Introduced z-scores for vital signs.- Information about the subject diary was expanded to clarify the requirements for diary completion.- The lower limit of the age range for this protocol was eliminated to allow for potential enrollment of children under 1 year of age.- Weaning algorithms for toilet trained and untrained children were revised and a dehydration assessment was added.
06 October 2015	<ul style="list-style-type: none">- Administration of investigational product was modified to allow for a dose adjustment at Week 12, if warranted based on subjects' weight gain/loss over the initial 12-week treatment period.- Urine and stool collection will be done for 48 hours prior to all scheduled visits (phone and clinic) rather than for 72 hours.- Specifications for the management of nutritional support were updated based on expert opinion.
25 February 2016	<ul style="list-style-type: none">- Capture of output diary data was limited to 48 hours prior to every clinic visit and phone visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported