



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 |
|-----------------------|-------------|

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 |
|------------------|----------------------------|

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 |
|------------------|------------------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

End point timeframe:

| |
|--|
| From start of study treatment up to 28 weeks |
|--|

| 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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

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.

| 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