Clinical trial results:
Phase 3, Multicenter, Randomized Study with 2 Different Doses of Prucalopride Administered to Male and Female Pediatric Subjects Aged 6 Months to 17 years with Functional Constipation, Consisting of a 12-week Double-blind, Placebo-controlled Part (Part A) to Evaluate Efficacy and Safety Followed by a 36-week Double-blind Extension Part (Part B) to Document Long-term Safety up to Week 48

Summary

EudraCT number	2022-003221-22
Trial protocol	Outside EU/EEA
Global end of trial date	13 November 2023

Results information

Result version number	v1 (current)
This version publication date	26 May 2024
First version publication date	26 May 2024

Trial information

Trial identification

Sponsor protocol code	TAK-555-3010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04759833
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 November 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the efficacy of prucalopride during the 12-week double-blind, placebo-controlled treatment phase and long-term (48 weeks) safety and tolerability in toilet-trained participants with functional constipation who are at least 3 years of age.

Protection of trial subjects:

Each participant signed an informed consent form (ICF) before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 July 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	9 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 175
Worldwide total number of subjects	175
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	1
Children (2-11 years)	111
Adolescents (12-17 years)	63
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 42 investigative sites in the United States from 13 July 2021 to 13 November 2023.

Pre-assignment

Screening details:

175 participants were randomised in a 1:1:1 ratio to receive prucalopride at low/high dose/placebo in Part A of study per their body weight. All participants who completed Part A entered Part B, and those in placebo group of Part A were re-randomized based on their weight in 1:1 ratio to receive prucalopride at low/high dose in Part B of the study.

Period 1

Period 1 title	Placebo-controlled Period (12 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: Placebo

Arm description:

Participants weighing <50 kg drew equal volumes from two bottles of placebo oral solution to account for the daily dose assigned or participants weighing ≥50 kg received two placebo oral tablets, once daily (QD), during 12 weeks in Part A. Prucalopride matching placebo (oral solution or tablet) were dosed depending on the participant's body weight (BW) at the randomization visit.

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

Dosage and administration details:

Participants received matching placebo of oral solution or tablet QD.

Arm title	Part A: Low Dose Prucalopride

Arm description:

Participants weighing <50 kg received 0.04 milligrams per kilogram (mg/kg) of prucalopride oral solution (drew the required volume from one bottle of 0.4 milligram per milliliter [mg/mL] and one bottle of placebo oral solution), QD or participants weighing ≥50 kg received one 2 milligram (mg) of prucalopride oral tablet and one placebo oral tablet, QD, during 12 weeks in Part A. Prucalopride (oral solution or tablet) were dosed depending on the participant's BW at the randomization visit.

Arm type	Experimental
Investigational medicinal product name	Prucalopride
Investigational medicinal product code	
Other name	TAK-555, Prucalopride succinate
Pharmaceutical forms	Tablet, Oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants received 0.04 mg/kg or 0.08 mg/kg oral solution or 2 mg oral tablet of prucalopride QD.

Arm title	Part A: High Dose Prucalopride

Arm description:

Participants weighing <50 kg received 0.08 mg/kg of prucalopride oral solution (drew the required volume from two bottles of 0.4 mg/mL to account for the daily dose assigned), QD or participants weighing ≥50 kg received two 2 mg of prucalopride oral tablets, QD, during 12 weeks of treatment period in Part A. Prucalopride (oral solution or tablet) were dosed depending on the participant's BW at the randomization visit.

Arm type	Experimental
Investigational medicinal product name	Prucalopride
Investigational medicinal product code	
Other name	TAK-555, Prucalopride succinate
Pharmaceutical forms	Tablet, Oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants received 0.04 mg/kg or 0.08 mg/kg oral solution or 2 mg oral tablet of prucalopride QD.

Number of subjects in period 1	Part A: Placebo	Part A: Low Dose Prucalopride	Part A: High Dose Prucalopride
Started	56	60	59
Completed	46	49	39
Not completed	10	11	20
Noncompliance with Study Drug	-	-	1
Physician decision	-	1	-
Adverse event, non-fatal	1	4	2
Withdrawal of Consent by Participant	5	3	9
Study Terminated by Sponsor	-	2	3
Lost to follow-up	4	1	4
Lack of efficacy	-	-	1

Period 2

Period 2 title	Safety Extension Period (40 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Part B: Low Dose Prucalopride

Arm description:

Participants weighing <50 kg received 0.04 mg/kg of prucalopride oral solution (drew the required volume from one bottle of 0.4 mg/mL and one bottle of placebo oral solution to account for the daily dose assigned), QD or participants weighing ≥50 kg received one 2 mg of prucalopride oral tablet and one placebo oral tablet, QD, for 36 weeks during the 40-week Part B Period. Prucalopride (oral solution or tablet) were dosed depending on the participant's BW at the randomization visit.

Arm type	Experimental

Investigational medicinal product name	Prucalopride
Investigational medicinal product code	
Other name	TAK-555, Prucalopride succinate
Pharmaceutical forms	Tablet, Oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants received 0.04 mg/kg or 0.08 mg/kg oral solution or 2 mg oral tablet of prucalopride QD.

Arm title	Part B: High Dose Prucalopride

Arm description:

Participants weighing <50 kg received 0.08 mg/kg of prucalopride oral solution (drew the required volume from two bottles of 0.4 mg/mL to account for the daily dose assigned), QD or participants weighing ≥50 kg received two 2 mg of prucalopride oral tablets, QD, for 36 weeks during the 40-week Part B Period. Prucalopride (oral solution or tablet) were dosed depending on the participant's BW at the randomization visit.

Arm type	Experimental
Investigational medicinal product name	Prucalopride
Investigational medicinal product code	
Other name	TAK-555, Prucalopride succinate
Pharmaceutical forms	Tablet, Oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants received 0.04 mg/kg or 0.08 mg/kg oral solution or 2 mg oral tablet of prucalopride QD.

Number of subjects in period 2	Part B: Low Dose Prucalopride	Part B: High Dose Prucalopride
Started	72	62
Completed	37	28
Not completed	35	34
Adverse event, non-fatal	1	1
Withdrawal of Consent by Participant	4	8
Study Terminated by Sponsor	21	16
Lost to follow-up	1	3
Reason not Specified	8	5
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part A: Placebo
Reporting group description:	
Participants weighing <50 kg drew equal volumes from two bottles of placebo oral solution to account for the daily dose assigned or participants weighing ≥50 kg received two placebo oral tablets, once daily (QD), during 12 weeks in Part A. Prucalopride matching placebo (oral solution or tablet) were dosed depending on the participant's body weight (BW) at the randomization visit.	
Reporting group title	Part A: Low Dose Prucalopride
Reporting group description:	
Participants weighing <50 kg received 0.04 milligrams per kilogram (mg/kg) of prucalopride oral solution (drew the required volume from one bottle of 0.4 milligram per milliliter [mg/mL] and one bottle of placebo oral solution), QD or participants weighing ≥50 kg received one 2 milligram (mg) of prucalopride oral tablet and one placebo oral tablet, QD, during 12 weeks in Part A. Prucalopride (oral solution or tablet) were dosed depending on the participant's BW at the randomization visit.	
Reporting group title	Part A: High Dose Prucalopride
Reporting group description:	
Participants weighing <50 kg received 0.08 mg/kg of prucalopride oral solution (drew the required volume from two bottles of 0.4 mg/mL to account for the daily dose assigned), QD or participants weighing ≥50 kg received two 2 mg of prucalopride oral tablets, QD, during 12 weeks of treatment period in Part A. Prucalopride (oral solution or tablet) were dosed depending on the participant's BW at the randomization visit.	

Reporting group values	Part A: Placebo	Part A: Low Dose Prucalopride	Part A: High Dose Prucalopride
Number of subjects	56	60	59
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	9.4	9.8	9.8
standard deviation	± 3.73	± 4.00	± 3.96
Gender categorical Units: Subjects			
Female	35	28	28
Male	21	32	31
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	23	28	30
Not Hispanic or Latino	33	32	29
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	23	22	23
White	31	34	35
More than one race	0	2	0
Unknown or Not Reported	2	1	0

Region of Enrollment Units: Subjects			
United States United States	56	60	59
Weight Units: kg			
arithmetic mean	44.24	47.24	43.72
standard deviation	± 25.318	± 24.326	± 23.793
Body Mass Index (BMI)			
BMI = weight (kg)/[height (m)^2]			
Units: kilograms per meter square (kg/m^2)			
arithmetic mean	20.76	21.63	20.44
standard deviation	± 6.702	± 6.461	± 6.255
Height Units: centimeter (cm)			
arithmetic mean	139.86	142.57	140.35
standard deviation	± 23.563	± 22.480	± 24.554

Reporting group values	Total		
Number of subjects	175		
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	91		
Male	84		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	81		
Not Hispanic or Latino	94		
Unknown or Not Reported	0		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	68		
White	100		
More than one race	2		
Unknown or Not Reported	3		
Region of Enrollment Units: Subjects			
United States United States	175		

Weight Units: kg arithmetic mean standard deviation	- -		
Body Mass Index (BMI)			
BMI = weight (kg)/[height (m)^2]			
Units: kilograms per meter square (kg/m^2) arithmetic mean standard deviation	- -		
Height Units: centimeter (cm) arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Part A: Placebo

Reporting group description:

Participants weighing <50 kg drew equal volumes from two bottles of placebo oral solution to account for the daily dose assigned or participants weighing ≥50 kg received two placebo oral tablets, once daily (QD), during 12 weeks in Part A. Prucalopride matching placebo (oral solution or tablet) were dosed depending on the participant's body weight (BW) at the randomization visit.

Reporting group title	Part A: Low Dose Prucalopride

Reporting group description:

Participants weighing <50 kg received 0.04 milligrams per kilogram (mg/kg) of prucalopride oral solution (drew the required volume from one bottle of 0.4 milligram per milliliter [mg/mL] and one bottle of placebo oral solution), QD or participants weighing ≥50 kg received one 2 milligram (mg) of prucalopride oral tablet and one placebo oral tablet, QD, during 12 weeks in Part A. Prucalopride (oral solution or tablet) were dosed depending on the participant's BW at the randomization visit.

Reporting group title	Part A: High Dose Prucalopride

Reporting group description:

Participants weighing <50 kg received 0.08 mg/kg of prucalopride oral solution (drew the required volume from two bottles of 0.4 mg/mL to account for the daily dose assigned), QD or participants weighing ≥50 kg received two 2 mg of prucalopride oral tablets, QD, during 12 weeks of treatment period in Part A. Prucalopride (oral solution or tablet) were dosed depending on the participant's BW at the randomization visit.

Reporting group title	Part B: Low Dose Prucalopride

Reporting group description:

Participants weighing <50 kg received 0.04 mg/kg of prucalopride oral solution (drew the required volume from one bottle of 0.4 mg/mL and one bottle of placebo oral solution to account for the daily dose assigned), QD or participants weighing ≥50 kg received one 2 mg of prucalopride oral tablet and one placebo oral tablet, QD, for 36 weeks during the 40-week Part B Period. Prucalopride (oral solution or tablet) were dosed depending on the participant's BW at the randomization visit.

Reporting group title	Part B: High Dose Prucalopride

Reporting group description:

Participants weighing <50 kg received 0.08 mg/kg of prucalopride oral solution (drew the required volume from two bottles of 0.4 mg/mL to account for the daily dose assigned), QD or participants weighing ≥50 kg received two 2 mg of prucalopride oral tablets, QD, for 36 weeks during the 40-week Part B Period. Prucalopride (oral solution or tablet) were dosed depending on the participant's BW at the randomization visit.

Primary: Parts A and B: Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs)

End point title	Parts A and B: Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs)[1]

End point description:

Adverse event (AE) = any untoward medical occurrence in clinical investigation participant administered pharmaceutical product that did not necessarily have causal relationship with this treatment. TEAE = any event emerging/manifesting at/after initiation of treatment with investigational product (IP)/medicinal product/any existing event that worsens in either intensity/frequency following exposure to IP/medicinal product. Serious adverse event (SAE) = any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization/prolongation of existing hospitalization, results in persistent/significant disability/incapacity, is congenital abnormality/birth defect, is important medical event. For Part A, Safety Analysis Set included all participants who received at least 1 dose of study drug in Part A. For Part B, the Safety Analysis Set included all participants who received at least 1 dose of study drug in Part B.

End point type	Primary

End point timeframe:

From first dose of study drug up to Week 52

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: No statistical analyses have been specified for this end point as they were not performed due to study termination based on futility.

End point values	Part A: Placebo	Part B: Low Dose Prucalopride	Part A: Low Dose Prucalopride	Part B: High Dose Prucalopride
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	72	60	62
Units: participants				
TEAEs	15	22	24	17
TESAEs	1	1	0	1

End point values	Part A: High Dose Prucalopride			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: participants				
TEAEs	18			
TESAEs	0			

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Change from Baseline in Average Number of Weekly Number of Spontaneous Bowel Movements (SBMs) at Week 12

End point title	Part A: Change from Baseline in Average Number of Weekly Number of Spontaneous Bowel Movements (SBMs) at Week 12[2]

End point description:

Spontaneous bowel movement was defined as a bowel movement that was not preceded within a period of 24 hours by the intake of rescue medication. The average change from baseline in number of SBMs per week derived from the (e-diary) data, in toilet-trained participants who were at least 3 years of age collected during the placebo-controlled part (Part A) was assessed. The Completers Analysis Set included all toilet-trained participants who were at least 3 years of age in the Modified Intent-to-treat Analysis Set (mITT) analysis set who had an average number of SBM available for all 12 weeks in the placebo-controlled part (Part A) of the study.

End point type	Primary

End point timeframe:

Baseline, Week 12

Notes:

[2] - 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: No statistical analyses have been specified for this end point as they were not performed due to study termination based on futility.

End point values	Part A: Placebo	Part A: Low Dose Prucalopride	Part A: High Dose Prucalopride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	18	11	
Units: SBMs per week				
arithmetic mean (standard deviation)	1.4 (± 1.90)	1.9 (± 2.67)	0.9 (± 1.44)	

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and B: Number of Participants With Clinically Significant Vital Sign Abnormalities

End point title	Parts A and B: Number of Participants With Clinically Significant Vital Sign Abnormalities[3]

End point description:

Vital signs included measurement of pulse rate, systolic, and diastolic blood pressure. Clinically significant vital signs assessment was based on investigator interpretation. Number of participants with clinically significant changes in vital signs were reported. For Part A, the Safety Analysis Set included all participants who received at least 1 dose of study drug in Part A. For Part B, the Safety Analysis Set included all participants who received at least 1 dose of study drug in Part B.

End point type	Primary

End point timeframe:

From first dose of study drug up to Week 52

Notes:

[3] - 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: No statistical analyses have been specified for this end point as they were not performed due to study termination based on futility.

End point values	Part A: Placebo	Part B: Low Dose Prucalopride	Part A: Low Dose Prucalopride	Part B: High Dose Prucalopride
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	72	60	62
Units: participants	0	0	0	0

End point values	Part A: High Dose Prucalopride			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and B: Number of Participants With Clinically Significant Abnormalities in Clinical Laboratory Parameters

End point title	Parts A and B: Number of Participants With Clinically Significant Abnormalities in Clinical Laboratory Parameters[4]

End point description:

Laboratory parameters included blood chemistry, hematology, and urinalysis. Clinically significant laboratory parameters assessment was based on investigator interpretation. Number of participants with clinically significant changes in laboratory parameters (included hematology, blood chemistry, and urinalysis) were reported. For Part A, the Safety Analysis Set included all participants who received at least 1 dose of study drug in Part A. For Part B, the Safety Analysis Set included all participants who received at least 1 dose of study drug in Part B.

End point type	Primary

End point timeframe:

From first dose of study drug up to Week 52

Notes:

[4] - 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: No statistical analyses have been specified for this end point as they were not performed due to study termination based on futility.

End point values	Part A: Placebo	Part B: Low Dose Prucalopride	Part A: Low Dose Prucalopride	Part B: High Dose Prucalopride
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	72	60	62
Units: participants	0	0	0	0

End point values	Part A: High Dose Prucalopride			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Primary: Parts A and B: Number of Participants With Clinically Significant Electrocardiogram (ECG) Abnormalities

End point title	Parts A and B: Number of Participants With Clinically Significant Electrocardiogram (ECG) Abnormalities[5]

End point description:

ECG included heart rhythm, heart rate, QRS intervals, QT intervals, RR intervals and corrected QT (QTc) intervals parameters measurement. Clinically significant ECG assessment was based on investigator interpretation. Number of participants with clinically significant changes in ECG were reported. For Part A, the Safety Analysis Set included all participants who received at least 1 dose of study drug in Part A. For Part B, the Safety Analysis Set included all participants who received at least 1 dose of study drug in Part B.

End point type	Primary

End point timeframe:

From first dose of study drug up to Week 52

Notes:

[5] - 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: No statistical analyses have been specified for this end point as they were not performed due to study termination based on futility.

End point values	Part A: Placebo	Part B: Low Dose Prucalopride	Part A: Low Dose Prucalopride	Part B: High Dose Prucalopride
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	72	60	62
Units: participants	0	0	0	0

End point values	Part A: High Dose Prucalopride			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change From Baseline in Participants' Weekly Stool Consistency Based on Bristol Stool Form Scale (BSFS) Score at Week 12 Categorized by Age

End point title	Part A: Change From Baseline in Participants' Weekly Stool Consistency Based on Bristol Stool Form Scale (BSFS) Score at Week 12 Categorized by Age

End point description:

BSFS is a 7-score visual scale to measure stool consistency,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. A score of 1 or 2=constipation while a score of 6 or 7=diarrhea. A better score (scores of 3 and 4 represent ideal stools as they are easy to defecate while not containing excess liquid, 5 indicates average consistency but lack of dietary fiber) would trend toward the middle of the scale(3 to 5). Daily scores were summed to obtain a weekly score ranging from 7 to 49 with higher scores indicating diarrhea. Data for this outcome measure is reported per age group bifurcation.mITT Analysis Set=all randomised participants who received at least 1 dose of study drug in Part A. Number of subjects analysed=participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Part A: Placebo	Part A: Low Dose Prucalopride	Part A: High Dose Prucalopride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	40	34	
Units: score on a scale				
arithmetic mean (standard deviation)				
Participants <8 Years	-0.1 (± 16.56)	9.8 (± 12.75)	7.1 (± 6.31)	
Participants ≥8 Years	12.6 (± 16.77)	13.1 (± 21.15)	7.0 (± 10.44)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change From Baseline in Weekly Straining Score Based on a 3-point Likert Scale at Week 12

End point title	Part A: Change From Baseline in Weekly Straining Score Based on a 3-point Likert Scale at Week 12

End point description:

Straining was assessed based on a 3-point Likert scale: (1=not at all, 2=a little, 3=a lot). A higher score indicates a lot of straining i.e., worsening of the condition. Daily scores were summed to obtain a weekly score ranging from 7 to 21 with higher scores indicating a lot of straining. The mITT Analysis Set included all randomised participants who received at least 1 dose of the study drug in Part A. Number of subjects analysed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Part A: Placebo	Part A: Low Dose Prucalopride	Part A: High Dose Prucalopride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	40	34	
Units: score on a scale				
arithmetic mean (standard deviation)				
Participants ≥8 Years	-5.7 (± 8.49)	-5.2 (± 5.92)	-7.6 (± 5.12)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percentage of Responders Based on Assessment of SBMs

End point title	Part A: Percentage of Responders Based on Assessment of SBMs

End point description:

Spontaneous bowel movement was defined as a bowel movement that was not preceded within a period of 24 hours by the intake of rescue medication. Responder was defined as a participant having an

increase of ≥1 SBM per week compared to Baseline and ≥3 SBMs per week for at least 9 out of the 12 weeks of placebo-controlled part (Part A), including 3 of the last 4 weeks. Percentages are rounded off to the nearest single decimal place. The mITT Analysis Set included all randomised participants who received at least 1 dose of the study drug in Part A. Number of subjects analysed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline through Week 12

End point values	Part A: Placebo	Part A: Low Dose Prucalopride	Part A: High Dose Prucalopride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	56	55	
Units: percentage of responders				
number (not applicable)	1.9	3.6	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Percentage of Participants With Fecal Incontinence at Week 12

End point title	Part A: Percentage of Participants With Fecal Incontinence at Week 12

End point description:

Fecal incontinence was defined as unintentional smear or liquid stool in the underwear that is not due to poor wiping. Fecal incontinence can only occur in toilet-trained participants. Non-retentive fecal incontinence is diagnosed (must include at least a 1-month history in a child with a developmental age older than 4 years for all the following): (i) defecation in places inappropriate to the sociocultural context, (ii) no evidence of fecal retention, and (iii) after appropriate evaluation, the fecal incontinence cannot be explained by another medical condition. Percentages are rounded off to the nearest single decimal place. The mITT Analysis Set included all randomised participants who received at least 1 dose of the study drug in Part A. Number of subjects analysed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Week 12

End point values	Part A: Placebo	Part A: Low Dose Prucalopride	Part A: High Dose Prucalopride	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	33	30	
Units: percentage of participants				
number (not applicable)	12.9	3.0	16.7	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part A: Pharmacokinetic (PK) Plasma Concentrations of Prucalopride

End point title	Part A: Pharmacokinetic (PK) Plasma Concentrations of Prucalopride[6]

End point description:

The PK analysis set included all participants regardless of age in the safety analysis sets for whom at least 1 PK sample was evaluable. Number of subjects analysed is the number of participants with data available for analyses. 'n' signifies the number of participants with data available for analyses at the specified time point.

End point type	Other pre-specified

End point timeframe:

1 to 3 hours post-dose at Baseline (Day 0), 14 to 26 hours post-dose at Weeks 4, 8 and 12

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive pharmacokinetic data was collected and analysed for prucalopride arms only.

End point values	Part A: Low Dose Prucalopride	Part A: High Dose Prucalopride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	12		
Units: nanograms per milliliter (ng/ml)				
arithmetic mean (standard deviation)				
Baseline (1-3 Hours) [n=6,9]	4.707 (± 3.4659)	5.903 (± 4.0231)		
Week 4 (14 -26 Hours) [n=7,8]	2.607 (± 0.7336)	3.693 (± 2.0613)		
Week 8 (14 -26 Hours) [n=6,6]	2.343 (± 1.8725)	2.963 (± 2.0794)		
Week 12 (14 -26 Hours) [n=6,6]	4.365 (± 3.6288)	3.001 (± 4.5358)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to Week 52

Adverse event reporting additional description:

For Part A, the Safety Analysis Set included all participants who received at least 1 dose of study drug in Part A. For Part B, the Safety Analysis Set included all participants who received at least 1 dose of study drug in Part B.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26

Reporting groups

Reporting group title	Part A: Low Dose Prucalopride

Reporting group description:

Participants weighing <50 kg received 0.04 mg/kg of prucalopride oral solution (drew the required volume from one bottle of 0.4 mg/mL and one bottle of placebo oral solution), QD or participants weighing ≥50 kg received one 2 mg of prucalopride oral tablet and one placebo oral tablet, QD, during 12 weeks in Part A. Prucalopride (oral solution or tablet) were dosed depending on the participant's BW at the randomization visit.

Reporting group title	Part A: High Dose Prucalopride

Reporting group description:

Participants weighing <50 kg received 0.08 mg/kg of prucalopride oral solution (drew the required volume from two bottles of 0.4 mg/mL to account for the daily dose assigned), QD or participants weighing ≥50 kg received two 2 mg of prucalopride oral tablets, QD, during 12 weeks of treatment period in Part A. Prucalopride (oral solution or tablet) were dosed depending on the participant's BW at the randomization visit.

Reporting group title	Part A: Placebo

Reporting group description:

Participants weighing <50 kg drew equal volumes from two bottles of placebo oral solution to account for the daily dose assigned or participants weighing ≥50 kg received two placebo oral tablets, QD, during 12 weeks in Part A. Prucalopride matching placebo (oral solution or tablet) were dosed depending on the participant's BW at the randomization visit.

Reporting group title	Part B: High Dose Prucalopride

Reporting group description:

Participants weighing <50 kg received 0.08 mg/kg of prucalopride oral solution (drew the required volume from two bottles of 0.4 mg/mL to account for the daily dose assigned), QD or participants weighing ≥50 kg received two 2 mg of prucalopride oral tablets, QD, for 36 weeks during the 40-week Part B Period. Prucalopride (oral solution or tablet) were dosed depending on the participant's BW at the randomization visit.

Reporting group title	Part B: Low Dose Prucalopride

Reporting group description:

Participants weighing <50 kg received 0.04 mg/kg of prucalopride oral solution (drew the required volume from one bottle of 0.4 mg/mL and one bottle of placebo oral solution to account for the daily dose assigned), QD or participants weighing ≥50 kg received one 2 mg of prucalopride oral tablet and one placebo oral tablet, QD, for 36 weeks during the 40-week Part B Period. Prucalopride (oral solution or tablet) were dosed depending on the participant's BW at the randomization visit.

Serious adverse events	Part A: Low Dose Prucalopride	Part A: High Dose Prucalopride	Part A: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)	0 / 59 (0.00%)	1 / 56 (1.79%)

number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 59 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 60 (0.00%)	0 / 59 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional self-injury			
subjects affected / exposed	0 / 60 (0.00%)	0 / 59 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 60 (0.00%)	0 / 59 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part B: High Dose Prucalopride	Part B: Low Dose Prucalopride	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 62 (1.61%)	1 / 72 (1.39%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 62 (1.61%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 62 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intentional self-injury			
subjects affected / exposed	0 / 62 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 62 (0.00%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part A: Low Dose Prucalopride	Part A: High Dose Prucalopride	Part A: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 60 (28.33%)	10 / 59 (16.95%)	5 / 56 (8.93%)
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 60 (13.33%)	5 / 59 (8.47%)	3 / 56 (5.36%)
occurrences (all)	10	7	4
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	8 / 60 (13.33%)	4 / 59 (6.78%)	2 / 56 (3.57%)
occurrences (all)	8	4	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 60 (5.00%)	1 / 59 (1.69%)	1 / 56 (1.79%)
occurrences (all)	4	1	1

Non-serious adverse events	Part B: High Dose Prucalopride	Part B: Low Dose Prucalopride	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 62 (12.90%)	9 / 72 (12.50%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 62 (8.06%)	3 / 72 (4.17%)	
occurrences (all)	6	3	
Gastrointestinal disorders			
Vomiting			

subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 2	0 / 72 (0.00%) 0	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 1 / 62 (1.61%) 1	 7 / 72 (9.72%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2020	The following changes were made as per Amendment 1: 1) Clarified that the primary endpoint was based on data collected during the placebo-controlled part (Part A). 2) Corrected text describing Part B of the study as placebo-controlled. 3) Corrected the population used for the primary estimand of interest from Intent-to-Treat (ITT) to mITT. 4) Corrected the number of bowel movements (BMs) from greater than (>)3 to ≥3.
20 October 2021	The following changes were made as per Amendment 2: 1) Added that if a participant weighing ≥50 kg could not tolerate the tablets, they could be switched to oral solution for the duration of study participation. Further, switching from oral solution to tablets was not allowed. 2) Revised the frequency for providing rescue medications to align with operational processes. 3) Aligned the screening visit window with wording in the protocol. 4) Added patient global impression of severity (PGI-S) and caregiver global impression of severity (CGI-S) assessments at screening. 5) Specified that if a participant chose to withdraw from study participation due to personal concerns or unavoidable circumstances related to the coronavirus disease 2019 (COVID-19) pandemic (other than a COVID-19–related AE), this had to be specified as the reason for participant withdrawal in the electronic case report form (eCRF). 6) Added details on the anchor-based analysis. 7) Added details of COVID-19-related flexibility in study conduct.
27 October 2022	The following changes were made as per Amendment 3: 1) Updated the exploratory endpoints on "proportion of participants with an average of ≥3 (S)BMs per week and increase of ≥1 (S)BM compared to baseline during a 12-week double-blind, placebo-controlled treatment phase" and "proportion of participants with an average of ≤1 (S)BMs per week during the 12-week double-blind, placebo-controlled treatment phase" to only evaluate SBMs, not BMs. 2) Updated the duration of the study from approximately 60 to approximately 52 months (or from 3-4 to 4-4.5 years of age). 3) Corrected the duration of the screening period from approximately 21 - 33 days (and maximum duration of participation, where mentioned, from 55 - 56 weeks). 4) Added a reminder to check whether the participant had experienced any psychiatric changes throughout the study. 5) Corrected to indicate that restrictions related to lifestyle modifications (including dietary changes) were applicable from randomization onwards and to include the specification that study-allowed rescue medication was not restricted. 6) Added a new section describing what actions should be taken in case of suicidal ideation (SI)/suicidal behavior (SIB).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 November 2023	Study was terminated as per the Data Monitoring Committee (DMC) decision owing to futility with no safety concerns.	-

Notes:

Limitations and caveats

None reported