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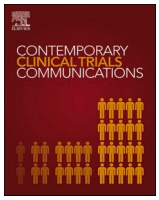

Design of a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of prucalopride in pediatric patients with functional constipation

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ABSTRACT

Background: A previous phase 3 trial of prucalopride in pediatric patients (6 months–18 years old) with functional constipation (FC) demonstrated no efficacy versus placebo. We designed an additional phase 3 trial to further assess the efficacy, long-term safety and tolerability of prucalopride in children and adolescents.
Methods: This multicenter trial (ClinicalTrials.gov identifier: NCT04759833; EudraCT number: 2022-003221-22) comprises a 12-week, randomized, double-blind, placebo-controlled phase, followed by a 36-week, double-blind, safety extension phase. Approximately 240 toilet-trained patients aged 3–17 years will be randomized 1:1:1 to receive low- (0.04 mg/kg) or high-dose (0.08 mg/kg) prucalopride, or placebo once daily. Fifteen non-toilet-trained patients ≥6 months old with FC will be included in an exploratory efficacy and safety analysis.
Discussion: The efficacy endpoints used in this study will differ from those used in adults and in the previous pediatric phase 3 trial; they have been adapted to be more suitable for a wider age range of pediatric patients. Both study phases will be longer than in the previous pediatric study, providing a longer time period in which to assess the efficacy and safety of prucalopride. Study participants will be identified using the modified Rome IV criteria for FC, instead of the Rome III criteria, and non-toilet-trained patients will be included, which will broaden the population of pediatric patients assessed. Patients will undergo fecal disimpaction before randomization and undergo standardized continuous behavioral therapy throughout the trial. This pediatric study of prucalopride will aim to demonstrate the efficacy and long-term safety of this treatment.

1. Introduction

In children and adolescents aged 2–17 years, chronic idiopathic constipation or functional constipation (CIC or FC) has a mean global prevalence of approximately 14% [1]. Symptoms include infrequent, painful defecation and abdominal pain, with no underlying medical condition responsible for constipation [2]. Furthermore, owing to the high variability of the severity of FC, a complete cessation of spontaneous bowel movements (SBMs) may occur in some patients [3].

Current treatments for children and adolescents with FC include behavioral modification, toilet training, and oral and/or rectal laxatives [4,5]. Despite these treatment options, the quality of care is limited owing to a lack of guidance for disease management, a poorly defined disease state and insufficient clinical trial data on drug therapies; thus, complete and sustainable symptomatic relief remains a major unmet medical need for pediatric patients [6]. Previous studies in children and adolescents with FC identified an insufficient response to conventional treatment (symptoms persisted in ~33–40% of patients) and relapses were common [4]. Additional treatment options for long-term management of this disease are therefore necessary.

Prucalopride is a selective serotonin type 4 receptor agonist indicated for the treatment of CIC in adults [7]; it demonstrated efficacy in the treatment of CIC in adults, with a favorable safety and tolerability profile [7,8]. A phase 1, open-label, 8-week, noncontrolled study of the pharmacokinetics (PK), efficacy, safety and tolerability of prucalopride in 37 children and adolescents aged 4–12 years with FC also reported a

Abbreviations: BM, bowel movement; CIC, chronic idiopathic constipation; DMC, data monitoring committee; ECG, electrocardiogram; FC, functional constipation; FDA, US Food and Drug Administration; PEG, polyethylene glycol; PK, pharmacokinetics; SBM, spontaneous bowel movement.

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favorable efficacy and tolerability profile [9]. However, a phase 3, randomized, controlled trial of prucalopride in 213 pediatric patients with FC aged 6 months to 18 years demonstrated no efficacy versus placebo (ClinicalTrials.gov identifier: NCT01330381) [10]. Prucalopride was generally well tolerated in pediatric patients in that study, and a population PK analysis indicated that the PK profile of prucalopride in pediatric patients was similar to that observed in adults [11]. Therefore, any difference in prucalopride exposure between adults, children and adolescents could not account for the lack of efficacy versus placebo [9,11].

Limitations of this previous phase 3 study included the restrictive primary efficacy endpoints (proportion of patients with a mean frequency of ≥3 SBMs per week and ≤1 episode of fecal incontinence every 2 weeks over weeks 5–8 of the double-blind phase) [10], which were not suitable for a wide age range of pediatric patients. Fecal incontinence can only occur in toilet-trained patients; non-retentive fecal incontinence can be diagnosed in children with a developmental age older than 4 years [12]. An additional limitation was that the efficacy and safety of prucalopride were assessed over a relatively short period (double-blind phase, 8 weeks; extension phase, 24 weeks). Lastly, study participants were identified using older diagnostic criteria for FC (the Rome III criteria 2006) [12]. The updated Rome IV criteria (2016) shortened the duration of symptoms needed to fulfill the criteria for FC from 2 months to 1 month [12–14].

Prucalopride was approved in the USA in 2018 for the treatment of CIC in adults. To fulfill two US Food and Drug Administration (FDA) post-marketing requirements and the Pediatric Research Equity Act, we designed the phase 3 trial described here in consultation with the FDA. This trial will assess the efficacy and long-term safety of prucalopride in children and adolescents.

2. Methods

2.1. Trial design

This phase 3, multicenter trial (ClinicalTrials.gov identifier: NCT04759833; EudraCT number: 2022-003221-22), which is currently in the recruitment phrase, comprises a 12-week, randomized, double-blind, placebo-controlled phase, followed by a 36-week, double-blind, safety extension phase. The study will be conducted at approximately 40–45 sites in the USA. A screening period will be conducted 10–33 days before randomization for the 12-week, placebo-controlled phase. All patients will undergo fecal disimpaction before randomization and will be supplied with the appropriate dose of polyethylene glycol (PEG) 3350 with or without electrolytes (1–1.5 g/kg/day divided into two doses for 3–6 consecutive days) until a watery stool is passed. If a watery stool is not passed, this step may be repeated once. For patients aged 2 years and older with either difficulties swallowing or an unsuccessful initial disimpaction, sodium phosphate enemas may be given once daily for up to 3 days (recommended dose for patients ≤18 years: 2.5 mL/kg with a max dose of 133 mL/dose). The instructions follow the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition's recommendations (2014) [2]; however, investigators are allowed to follow their hospital/office protocols. Staff at the study site will call the patient or patient's parent/caregiver to determine if disimpaction was successful 1–2 days after the procedure. Additionally, the investigator may perform an optional rectal examination at the screening or baseline visits to confirm the presence/absence of fecal impaction. All patients will also undergo standardized continuous behavioral therapy to mitigate the effect of withholding behavior throughout the trial, which includes education of patients aged 3 years or older at randomization and parents, on the importance of positive reinforcement, toilet routine and correct toilet position.

Approximately 240 toilet-trained patients aged 3–17 years will be randomized 1:1:1 (~80 patients per treatment arm) to receive low- (0.04 mg/kg) or high-dose (0.08 mg/kg) prucalopride, or placebo once daily for 12-weeks (Fig. 1). Fifteen non-toilet-trained patients aged at least 6 months with FC will also be enrolled and included in exploratory efficacy and safety analyses. Following the 12-week, placebo-controlled phase, patients receiving placebo will be re-randomized 1:1 to receive low- or high-dose prucalopride once daily for the 36-week, double-blind, safety extension phase. Patients receiving prucalopride will continue on their previous dose. Patients will receive a follow-up call 4 weeks after the final prucalopride dose.

The dose of prucalopride will depend on the patient's body weight at randomization. In both the 12-week placebo-controlled phase and 36-week safety extension phase, patients weighing less than 50 kg in the low-dose group will receive the oral solution of prucalopride daily (0.04 mg/kg; drawing equal volumes from one bottle of prucalopride and one bottle of placebo oral solutions); patients weighing 50 kg or more will receive one tablet of prucalopride (2.0 mg) and one tablet of placebo daily. Patients weighing less than 50 kg at baseline may undergo a dose adjustment for the oral solution of prucalopride based on their weight at week 24. In both the 12-week placebo-controlled phase and 36-week safety extension phase, patients weighing less than 50 kg in the high-dose group will receive the oral solution of prucalopride daily (0.08 mg/kg; drawing equal volumes from two bottles of prucalopride oral solution); patients weighing 50 kg or more will receive two tablets of prucalopride daily (2 × 2.0 mg). In the 12-week placebo-controlled phase, patients weighing less than 50 kg in the placebo group will receive twice the equal volume from two bottles of placebo oral solution, and patients weighing 50 kg or more will receive two tablets of placebo daily. As the majority of patients increased their dose from 0.02 mg/kg to 0.06 mg/kg in the previous pediatric study [10] and because the current study includes a high-dose group (0.08 mg/kg oral solution or two 2-mg tablets), optional dose escalations were not deemed necessary.

When approximately 50% of toilet-trained patients (n = 120) have completed the 12-week, placebo-controlled phase, an interim analysis will be performed to determine if the study should be continued/terminated based on futility. A second interim analysis will be performed when 100% of toilet-trained patients (n = 240) have completed or withdrawn from the 12-week, placebo-controlled phase to determine if the safety extension phase should be continued/terminated. An independent data monitoring committee (DMC) will monitor the safety data in this study and will assess if the efficacy is sufficient for study continuation. The DMC, which will include three clinicians (of which, at least one will be a pediatrician), a PK expert and a statistician, will be involved in both planned interim analyses. The DMC is independent and will provide recommendations to the sponsor regarding the continuation or termination of the study. Owing to a study design with a single protocol combining both efficacy and long-term safety endpoints, this interim analysis will minimize any risk of exposing children and adolescents to prucalopride if it does not demonstrate treatment benefit versus placebo. Based on the primary efficacy endpoint, both the low- and high-dose treatment arms will need to have a conditional power of less than 20% versus placebo to terminate the study based on futility.

During the placebo-controlled phase, on-site visits are scheduled for the baseline visit and weeks 4, 8 and 12, with telephone contacts scheduled for the other weeks of this phase. At each contact, checks will be made for adverse events, fecal incontinence, prohibited and concomitant medications, and concomitant surgeries/procedures. Additionally, at the on-site visits, targeted physical examinations will take place (height, weight, respiratory, cardiovascular and abdominal examinations, and an optional examination of the perianal region if clinically indicated/at the discretion of the investigator), along with behavioral therapy reminders, laboratory and retentive posturing assessments. A 12-lead electrocardiogram (ECG) will take place at baseline and week 12.

In the safety extension phase, on-site visits are scheduled for weeks 16, 24, 32, 40 and 48, with telephone contacts scheduled for weeks 20, 28, 36 and 44. At each contact, checks will be made for adverse events, fecal incontinence, toilet training status, prohibited and concomitant

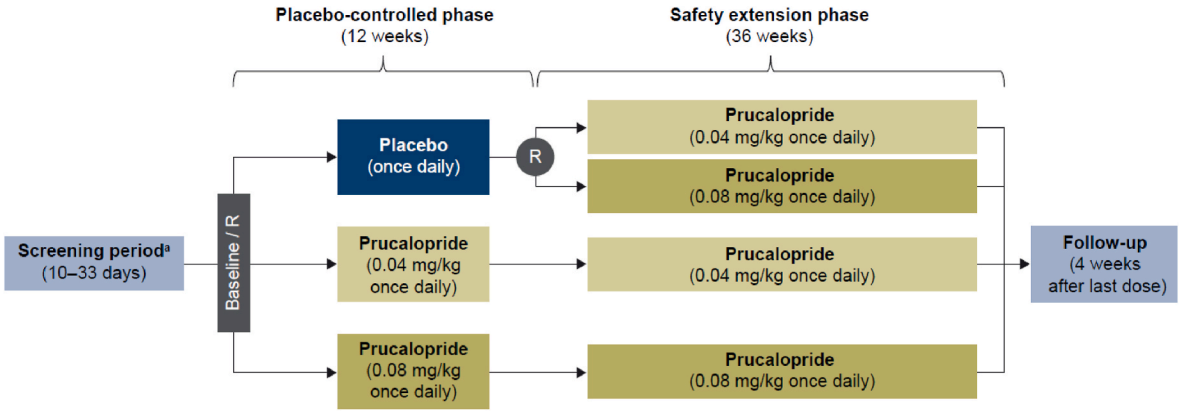

Fig. 1. Study design.
[a]During the screening period, all patients will undergo fecal disimpaction. If clinically indicated, a rectal examination may be performed to confirm the absence or presence of fecal impaction at the screening or the baseline visits; an anal and cremasteric reflex examination is also optional. Within 1 week of successful disimpaction, patients will be randomized to one of the treatment arms. If fecal impaction is still detected and repeating the assessment would occur outside of the screening period, the patient will be allowed to re-screen.
R, randomization.

medications, and concomitant surgeries/procedures. Additionally, at the on-site visits, targeted physical examinations (weight, respiratory, cardiovascular and abdominal examinations; and an optional examination of the perianal region if clinically indicated/at the discretion of the investigator) will take place along with behavioral therapy reminders. A 12-lead ECG will be performed at weeks 16, 32 and 48.

Rescue medication will be permitted if no bowel movements (BMs) occur within a 72-h period. Permitted rescue medications are bisacodyl tablets (5 mg) or suppositories (10 mg) during both study phases, or oral PEG 3350 during the safety extension phase only. For patients aged 6 months to 4 years, investigator discretion can be exercised regarding the use of other rescue medications. If the use of rescue medications, dose escalations and other alternative treatments remain ineffective, the investigator should contact the study monitor to assess the patient's continued participation in the study.

The study and all consent and assent documentation will be performed in accordance with the International Conference on Harmonisation and Good Clinical Practices guidelines.

2.2. Study participants

Toilet-trained patients aged 3–17 years, and non-toilet-trained patients aged at least 6 months will be eligible for inclusion. Other key inclusion criteria include: body weight of at least 5.5 kg; fulfillment of modified Rome IV criteria for FC [13,14]; and willingness to discontinue laxatives during the screening period and up to the disimpaction phase, with the exception of rescue medication if no BM has occurred within a 72-h period. Patients aged 6 months to 4 years must have ≤2 defecations per week and at least one of the following for at least 1 month: a history of excessive stool retention; a history of painful or hard BMs; a history of large diameter stools (in the diaper); or presence of a large fecal mass in the rectum. For toilet-trained patients, the following additional criteria may be used: ≥1 episode per week of incontinence; or a history of large diameter stools which may obstruct the toilet. Patients aged older than 4 years must have ≤2 defecations per week and at least one of the following for at least 1 month: ≥1 episode of fecal incontinence per week (in patients with toileting skills); a history of retentive posturing or excessive volitional stool retention; a history of painful or hard BMs; presence of large fecal mass in the rectum; or a history of large diameter stools that may obstruct the toilet.

Key exclusion criteria will be: abnormal ECG findings; major cardiovascular disease (including cardiomyopathy, cardiac insufficiency, uncorrected congenital heart disease, symptomatic valve disorder or septal defects); physical or psychiatric illnesses; non-retentive fecal incontinence; intestinal obstruction due to structural/functional disorders of the gut wall, obstructive ileus or severe inflammatory conditions of the intestinal tract; any medication 5 days before screening; renal impairment; secondary causes of constipation; alcohol or substance abuse; participation in a clinical study in the 30 days before the study; treatment with prucalopride in the 10 days before the study; pregnancy; liver disease; and an inability to swallow the study drug.

2.3. Efficacy endpoints

The primary efficacy endpoint in toilet-trained patients (aged ≥3 years) will be the mean change from baseline in the number of SBMs per week over the 12-week, placebo-controlled phase (a BM is defined as spontaneous if not preceded within a period of 24 h by the intake of rescue medication).

Key secondary endpoints in toilet-trained patients (aged ≥3 years) will be: the mean change from baseline in stool consistency as measured by the Bristol Stool Form Scale score per week during the 12-week, placebo-controlled phase; the mean change from baseline in straining as measured by a 3-point Likert scale per week during the 12-week, placebo-controlled phase; and the proportion of patients with an increase of ≥1 SBM per week compared with baseline over the 12-week, placebo-controlled phase and ≥3 SBMs per week for at least 9 of the 12 weeks, including 3 of the last 4 weeks of the 12-week placebo-controlled phase. An additional secondary endpoint in this patient group will assess the proportion of patients with fecal incontinence per week during the 12-week, placebo-controlled phase.

2.4. Exploratory endpoints

The exploratory endpoints in toilet-trained patients (aged ≥3 years) will be: the mean change from baseline in abdominal pain score as measured by the Wong–Baker Faces Scale [15] and the Numerical Response Scale for patients younger than 8 years and those aged 8 years or older, respectively, per week during the 12-week, placebo-controlled phase; the proportion of patients with ≥3 SBMs per week and an increase of ≥1 SBM compared with baseline over the 12-week, placebo-controlled phase; the proportion of patients with ≤1 SBM per week over the 12-week, placebo-controlled phase; the proportion of patients with a mean of ≥1 day of rescue medication (bisacodyl tablets [5.0 mg], suppositories [10 mg] or oral PEG 3350 [PEG 3350 permitted during the 36-week safety extension phase only]) intake per week; the

proportion of patients with retentive posturing (defined as the attempt to preserve continence by vigorous contraction of the gluteal muscles; observed through tight legged, tiptoed and/or back-arching posture) at monthly visits during the 12-week, placebo-controlled phase (the patient and/or parent or caregiver will be asked whether retentive posturing occurred during the previous 4 weeks by the clinical investigator); changes from baseline to week 12 in the Patient Global Impression of Severity scale, the Caregiver Global Impression of Severity scale and the Pediatric Quality of Life Inventory Gas and Bloating module for patients with functional gastrointestinal disorders [16]; and the proportion of patients with two or fewer signs and symptoms from the Rome IV criteria [13,14] after the 12-week, placebo-controlled phase.

The exploratory endpoints in non-toilet-trained patients (aged ≥6 months) will be the proportion of patients with ≥3 SBMs per week and an increase of ≥1 SBM per week compared with baseline; the number of SBMs per week (in categories ≤1 and > 1); and the mean change from baseline in stool consistency as measured by the Bristol Stool Form Scale score per week.

2.5. Safety endpoints

Safety assessments will be conducted by monitoring treatment-emergent adverse events, laboratory test abnormalities, ECG findings, vital signs findings and physical examinations (height, weight, respiratory, cardiovascular and abdominal examinations; as well as an optional examination of the perianal region if clinically indicated/at the discretion of the investigator) throughout the placebo-controlled and safety extension phases.

2.6. PK endpoints

Sparse PK sampling will be conducted during the 12-week, placebo-controlled phase. Patients' plasma prucalopride concentrations will be pooled with previous pediatric data (0.03 mg/kg single-dose data from PRU-USA-12 [NCT01674166], 0.03 mg/kg once daily with sparse PK data from PRU-USA-24 [NCT01670669] and 0.04 mg/kg up to 2 mg once daily with sparse PK data from SHP555-303 [NCT01330381]). The resulting population PK model will be used to establish the PK properties following single and once daily multiple doses of 0.02, 0.04 and 0.06 mg/kg (with a maximal daily dose of 2 mg) and evaluate the PK and pharmacodynamic relationship of prucalopride in pediatric patients.

2.7. Statistical methods

All statistical analyses will be performed using SAS Version 9.4 or higher (SAS Institute, Cary, NC, USA). Missing data will be imputed using a hybrid imputation approach prior to the analysis of the primary efficacy endpoint, which will be analyzed using a mixed model for repeated measures. This will include treatment group, age group (<12 years, 12–17 years), study week, study week stratified by treatment group interaction (as fixed effects), and baseline number of SBMs per week (≤1, >1; as a covariate and patient as a random effect). An unstructured variance-covariance matrix will be used to model the within-patient errors for both treatment groups. The p value for treatment differences in least squares means between the prucalopride and placebo groups after 12 weeks and associated 95% confidence interval from the multiple imputed datasets will be combined using Rubin's rules, as implemented in the PROC MIANALYZE procedure [17]. A minimum clinically important difference for the primary efficacy endpoint was estimated using data from the previous pediatric study of prucalopride (ClinicalTrials.gov identifier: NCT01330381) [10]. For this, the change from baseline in number of SBMs per week was estimated per outcome score of the global evaluation of efficacy of treatment scale (which was used as the anchor) after 8 weeks of treatment. This scale had 5 outcome scores: 'not at all', 'a little bit', 'moderately', 'quite a bit', and 'extremely' effective. If we consider a 'moderate' efficacy of treatment as a minimum clinically important difference, it was shown that in those patients, a mean change from baseline of 1.37 SBMs per week is observed. Across the six key efficacy studies with prucalopride in adults [8], a treatment difference of 1.66 SBMs per week for the subgroup of patients with <3 SBMs per week at baseline was observed. Based on this information and since this is a pediatric study, a difference of 1.40 SBMs per week between the prucalopride arm and placebo arm was chosen as a clinically meaningful treatment effect for the sample size estimation. The sample size was estimated through statistical simulations based on the Hochberg step-up procedure to control the type I error rate for the primary efficacy endpoint. These simulations showed that with 80 toilet-trained patients who are aged 3 years or older per treatment arm, the placebo-controlled part of the study will have at least 90% power to detect a treatment difference of 1.40 SBMs per week in the primary efficacy endpoint between at least one active dose of prucalopride and placebo assuming a pooled standard deviation of 2.5, using a two-sided two-sample *t*-test at a significance level of 5%.

The continuous secondary endpoints will be analyzed using a mixed model for repeated measures with the same covariates and factors as for the primary endpoint. The binary secondary endpoints will be analyzed using the Cochran–Mantel–Haenszel test to control the stratified age groups and baseline number of SBMs per week. An overall combined p value, response rates and differences in response rates, including 95% confidence intervals, will be derived using Rubin's rules, as implemented in the PROC MIANALYZE procedure [17]; the Cochran–Mantel–Haenszel test statistic will be normalized using the Wilson–Hilferty transformation before combining p values.

To account for the global family-wise error rate ($\alpha = 0.05$) for primary and key secondary endpoints, a Hochberg-step-up procedure will be used [18].

3. Discussion

FC is a common pediatric problem for which conventional treatments have limited effectiveness [2,4]. Children and adolescents with FC more commonly experience infrequent defecation accompanied by fecal incontinence due to fecal impaction than adults with FC [10]. Therefore, effective treatment should aim to increase the frequency of defecation and decrease fecal incontinence.

Findings from a phase 1 trial in children and adolescents with FC suggested the PK profile of a single dose of prucalopride was similar to that in adults [9]. Additionally, this study found prucalopride to have a favorable efficacy and tolerability profile in pediatric patients. However, a larger phase 3 study found no difference in efficacy between prucalopride and placebo in this patient population [10].

In addition to fulfilling FDA post-marketing requirements, the design of this study focuses on assessing the efficacy and safety of prucalopride in children and adolescents and addressing limitations of the previous phase 3 pediatric study [10]. This previous multicenter, randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of prucalopride in pediatric patients (6 months–18 years old) who received prucalopride or placebo once daily for 8 weeks. Findings showed that the proportion of responders and the incidence of treatment-emergent adverse events were similar between patients receiving prucalopride or placebo.

Importantly, the efficacy endpoints used in the present study will differ from those used in adults and in the previous pediatric phase 3 study, and have been adapted to be more suitable for a wider age range of pediatric patients. The primary efficacy endpoint of this study will be less restrictive than in the previous phase 3 study (the mean change in the number of SBMs per week over 12 weeks versus the proportion of patients with a mean of ≥3 SBMs per week and ≤1 episode of fecal incontinence every 2 weeks over weeks 5–8 of the double-blind phase [10]). However, treatment success for the primary efficacy endpoint is not defined as no longer fulfilling Rome IV criteria [13,14], but as an overall change in number of SBMs, which is a potential limitation of the

study. Additionally, the duration of both study phases will be longer than in the previous study (double-blind phase, 12 weeks versus 8 weeks; extension phase, 36 weeks versus 24 weeks), providing a longer period in which to assess the efficacy and safety of prucalopride. As efficacy data will not be collected during the 36-week safety extension phase, future studies will need to assess maintenance of response beyond 12 weeks.

In the present study, participants will be identified using the modified Rome IV criteria (2016) for FC, whereas in the previous phase 3 study, the Rome III criteria (2006) were used [12–14]. The modifications from the Rome III to Rome IV criteria included a decrease in the duration of symptoms required for diagnosis from 2 months to 1 month in children and adolescents; this is in accordance with the latest European and North American Societies for Pediatric Gastroenterology, Hepatology and Nutrition constipation guidelines [19]. This study will also include non-toilet-trained patients (aged ≥6 months), who were not included in the previous phase 3 study, and will therefore broaden the population of pediatric patients in which the efficacy and safety of prucalopride will be assessed.

Unsuccessful disimpaction at baseline could potentially affect the study findings and is a potential limitation; however, several procedures are in place to mitigate for this. Lastly, withholding behavior in children and adolescents with FC may lead to stool retention and secondary fecal incontinence due to fecal impaction or stool leakage from the rectum; this influence of behavioral factors may lead to misinterpretation of the study results. Because withholding behavior is a common pathophysiologic feature leading to changes in colonic function and the overall development of FC in children and adolescents [20], patients will undergo standardized continuous behavioral therapy throughout the trial. Should the study be inconclusive, a *post hoc* analysis examining patients with and without withholding behavior could be considered following a feasibility assessment, but is not currently planned.

To date, there are limited treatments that have demonstrated efficacy in pediatric patients with FC. The present study in this patient population has been robustly designed to address limitations of the previous phase 3 study and aims to assess the efficacy, long-term safety and tolerability of prucalopride.

CRediT authorship contributions

Carmen Cuffari: (conceptualization; roles/writing - original draft; writing - review and editing).

William Spalding: (conceptualization; methodology; roles/writing – original draft; writing - review and editing).

Heinrich Achenbach: (conceptualization; methodology; roles/writing - original draft; writing - review and editing).

Manoj Thakur: (conceptualization; methodology; roles/writing - original draft; writing - review and editing).

André Gabriel: (conceptualization; funding acquisition; investigation; methodology; roles/writing - original draft; writing - review and editing).

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Carmen Cuffari has nothing to disclose: William Spalding, Manoj Thakur and André Gabriel are employees of Takeda Development Center Americas, Inc. and stockholders of Takeda Pharmaceutical Company Ltd.

Heinrich Achenbach was an employee of Takeda Pharmaceuticals International AG at the time of the design of this study.

Data availability

No data was used for the research described in the article.

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