NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	210166/S-004
Priority or Standard	Standard
Submit Date(s)	October 1, 2024
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Division/Office	Division of Gastroenterology
Review Completion Date	July 9, 2025
Established/Proper Name	Prucalopride
Trade Name	Motegrity
Pharmacologic Class	5-HT_4 receptor agonist
Code name	--
Applicant	Takeda Pharmaceuticals U.S.A Inc.
Dosage form	Tablets (1 mg and 2 mg)
Applicant proposed Dosing Regimen	n/a
Applicant Proposed Indication(s)/Population(s)	n/a
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	n/a
Recommendation on Regulatory Action	Approval of labeling in Section 8.4 *Pediatric Use* to describe the results of a trial terminated early for futility in pediatric subjects aged 6 months to 17 years with functional constipation and fulfillment of PMRs 3529-1 and 3529-6

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DPMH=Division of Pediatric and Maternal Health
DPV=Division of Pharmacovigilance
OPDP=Office of Prescription Drug Promotion

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Prucalopride, a selective serotonin-4 (5-HT_4) receptor agonist, is a gastrointestinal (GI) prokinetic agent that stimulates colonic peristalsis (high-amplitude propagating contractions [HAPCs]), which increases bowel motility.

On December 14, 2018, Motegrity (prucalopride) was approved by the US Food and Drug Administration (FDA) for the treatment of chronic idiopathic constipation (CIC) in adults. Motegrity is supplied as film-coated tablets containing 1 mg of prucalopride (equivalent to 1.32 mg prucalopride succinate) or 2 mg of prucalopride (equivalent to 2.64 mg prucalopride succinate) for oral administration. The recommended dosage for adults with CIC is 2 mg once daily. The recommended dosage for patients with CIC with severe renal impairment (creatinine clearance [CrCL] less than 30 mL/min) is 1 mg once daily.

Motegrity was issued the following Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs) at the time of approval to assess the safety and efficacy of Motegrity for treatment of CIC (i.e., functional constipation (FC))[1] in pediatric patients.

PMR 3529-1 Evaluate the pharmacokinetics, efficacy, and safety of Motegrity (prucalopride) in pediatric patients with chronic idiopathic constipation (CIC) who are 6 months to less than 18 years of age by performing a randomized, double-blind, placebo-controlled, parallel group, 12-week treatment study.

PMR 3529-2 Assess the long-term safety of Motegrity (prucalopride) in pediatric patients with chronic idiopathic constipation (CIC) who are 6 months to less than 18 years of age and have completed a confirmatory efficacy and safety study with Motegrity (prucalopride) by performing an active comparator-controlled safety and tolerability study.

Given challenges with including an active comparator in the safety study (PMR 3529-2), the active comparator-controlled design was replaced with a design that evaluated two dose arms in a blinded study to assess the long-term safety and tolerability of prucalopride in pediatric patients with CIC. PMR 3529-2 was released on March 31, 2020, and replaced with PMR 3529-6 to reflect the change in study design.

[1] In clinical practice, chronic idiopathic constipation (CIC) and functional constipation (FC) are used interchangeably to refer to constipation that is characterized by a chronic time course and for which there are no anatomical, structural, or biochemical abnormalities. In pediatric patients, the term functional constipation is used more frequently.

PMR 3529-6 Assess the long-term safety of Motegrity (prucalopride) in pediatric patients with chronic idiopathic constipation (CIC) who are 6 months to less than 18 years of age and have completed a confirmatory efficacy and safety study with Motegrity (prucalopride) by performing a safety and tolerability study comparing two doses in a blinded design.

Study TAK-555-3010, entitled *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 B) to Document Long-term Safety up to Week 48,* was conducted to fulfill PMRs 3529-1 and 3529-6.

The Applicant's purpose in submitting this efficacy supplement was to provide the final clinical study report for Study TAK-555-3010, propose a labeling update to Section 8.4 *Pediatric Use* of the Prescribing Information (PI) to describe the study, and request changing the status of the PMRs 3529-1 and 3529-6 to fulfilled.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The efficacy of Motegrity for the treatment of CIC (i.e., FC) in pediatric subjects was evaluated in Study TAK-555-3010. The interim analysis of the primary endpoint showed that the number of spontaneous bowel movements (SBMs) per week over the 12-week double-blind period was similar in both the low and high dose prucalopride dose groups, as compared to the placebo group. The study met the prespecified stopping criteria (i.e., conditional power to demonstrate efficacy < 20% for each dose) for futility and the study was terminated early for futility. The final evaluation of efficacy was based on all subjects enrolled prior to the termination of the study and, consistent with the conclusions at the interim analysis, this evaluation did not provide evidence of efficacy for either the primary or secondary endpoints.

When evidence does not support the safety and effectiveness of a drug for an indication in pediatric patients because the results of studies conducted in the pediatric population were negative or inconclusive, an appropriate pediatric use statement must be added to the *Pediatric Use* subsection of the label to state that safety and effectiveness in pediatric patients have not been established.[2] Therefore, the labeling will be revised to add the required statement and a brief description of the findings from Study TAK-555-3010 to Section 8.4 *Pediatric Use*. PMRs 3529-1 and 3529-6 are considered fulfilled.

[2] 21 CFR 201.57(c)(9)(iv)(F)

1.3. Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• FC is a common condition experienced by children and adolescents. There is no known underlying organic cause, and the etiology is usually multifactorial. Contributing factors can include, but are not limited to, withholding behaviors (e.g., due to painful defecation), diet, and genetics. Untreated FC can negatively affect the child's or adolescent's quality of life and lead to further problems such as anal fissures or cystitis.	• FC can have a clinically significant impact on the health and well-being of children and adolescents.
Current Treatment Options	• On June 12, 2023, Linzess (linaclotide) was approved for the treatment of FC in pediatric patients 6 to 17 years of age. Linzess is the only FDA-approved treatment option for pediatric patients with FC. • Nonprescription osmotic laxatives (e.g., polyethylene glycol, lactulose, magnesium citrate), stimulant laxatives (e.g., senna, bisacodyl), lubricant laxatives (e.g., mineral oil), and stool softeners (e.g., docusate, mineral oil) are commonly used off-label for treatment of chronic or functional constipation in pediatric patients.	• There is an unmet medical need for safe and effective therapies for treatment of pediatric FC.
Benefit	• The Applicant conducted Study TAK-555-3010, a phase 3, multicenter, randomized study consisting of a 12-week double-blind, placebo-controlled part (Part A), followed by a 36-week double-blind safety extension part (Part B) to document safety and tolerability of prucalopride up to 48 weeks in pediatric subjects 6 months to 17 years of age with FC. • The primary endpoint was defined as the average change from baseline (CFB) in number of spontaneous bowel movements (SBMs) per week derived from the diary data over 12 weeks, collected	• The interim analysis indicated that the study met the criteria for futility (i.e., conditional power <20% for each dose) and was unlikely to demonstrate effectiveness; therefore, the study was terminated early for futility. • Based on the results of the primary and secondary endpoints, there is no evidence for the effectiveness of either prucalopride

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	during the placebo-controlled part (Part A). • The results of the interim analysis show that the mean CFB in SBM per week averaged over 12 weeks and averaged across 20 imputations was 1.76 in the placebo group, 2.13 in the prucalopride low dose group, and 1.11 in the prucalopride high dose group. • Using the statistical methods prespecified for the primary analysis of the primary endpoint in the SAP, the least squares (LS) Mean (95% CI) CFB of weekly SBM was 1.84 (1.34, 2.34) in the placebo group, 2.22 (1.73, 2.70) in the prucalopride low dose group, and 1.31 (0.82, 1.79) in the prucalopride high dose group. The LS Mean difference (95% CI) in CFB of weekly SBM during Part A, as compared to the placebo group, was 0.38 (-0.32, 1.07) in the prucalopride low dose group and -0.54 (-1.23, 0.16) in the prucalopride high dose group. The results of this Mixed Model with Repeat Measurements (MMRM) analysis do not provide evidence that either prucalopride dose had an effect on the frequency of SBMs. • The descriptive results for the secondary endpoints of CFB in (1) average weekly stool consistency and (2) straining at Week 12 showed that neither prucalopride dose group appeared to have a clinically meaningful effect on stool consistency or straining compared to placebo. • In addition, previous a phase 3 trial SPD555-303 conducted from April 2011 to March 2013 in Europe (ClinicalTrials.gov: NCT01330381) did not demonstrate efficacy of prucalopride in pediatric subjects with FC aged 6 months to < 18 years of age.[3] For additional information on this trial see	dose. • The safety and effectiveness of prucalopride for the treatment of FC in pediatric patients 6 months to 17 years of age has not been demonstrated.

[3] https://clinicaltrials.gov/study/NCT01330381

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Section 3.3 Additional Relevant History.	
Risk and Risk Management	• No deaths occurred in Study TAK-555-3010. The SAEs reported were depression, intentional self-injury, suicidal ideation, and abdominal pain, and the existing prucalopride labeling adequately addresses these risks. • In Part A, the most common treatment emergent adverse events (TEAEs) occurring in ≥2% of prucalopride-treated subjects and greater than placebo included headache, vomiting, upper respiratory tract infection, abdominal pain, pyrexia, pain in extremity, and seasonal allergy. • Headache, vomiting, and abdominal pain were reported as adverse reactions in ≥2% of prucalopride-treated subjects. in the double-blind, placebo-controlled trials of CIC in adults. • The AEs reported in pediatric patients that are not labeled in the adult population are common adverse events in this age group and are considered unlikely to be related to prucalopride.	• No new safety concerns were identified from the clinical study data nor postmarketing safety data. • Adverse reactions reported in pediatric patients 6 months to 17 years in Study TAK-555-3010 were similar to those reported in clinical trials of adults with CIC. • Routine postmarketing pharmacovigilance is recommended, with emphasis on psychiatric adverse events in pediatric patients.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	8.1.1 Trial Design, Electronic Diary (e-Diary)
		X	Observer reported outcome (ObsRO)	8.1.1 Trial Design, Electronic Diary (e-Diary)
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Functional Constipation (FC) is a common condition experienced by approximately 14% of children and adolescents in the US.[4] There is no known underlying organic cause and etiology is usually multifactorial. Contributing factors can include, but are not limited to, stool withholding behaviors (e.g., due to painful defecation), diet, and genetics. Untreated FC can negatively affect the child's or adolescent's quality of life and lead to further problems such as anal fissures or cystitis.

Diagnosis of FC is defined by the Rome diagnostic criteria, which are in their fourth edition (Rome IV) at the time of this review. Rome IV defines diagnosis of child and adolescent functional constipation as shown in Table 1.[5]

Table 1: Rome IV Diagnostic Criteria for Functional Constipation in Children/Adolescents

Must include two or more of the following occurring at least once per week for a minimum of 1 month with insufficient criteria for a diagnosis of Irritable Bowel Syndrome:
• Two or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years • At least one episode of fecal incontinence per week • History of retentive posturing or excessive volitional stool retention • History of painful or hard bowel movements • Presence of a large fecal mass in the rectum • History of large diameter stools which can obstruct the toilet • After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

Source: Adapted from https://theromefoundation.org/rome-iv/rome-iv-criteria/
Section H3a. Functional Constipation

Table 2: Rome IV Diagnostic Criteria for Functional Constipation in Infants/Toddlers (up to 4 years of age)

Must include one month of at least two of the following:
• Two or fewer defecations per week

[4] Robin, SG, C Keller, R Zwiener, PE Hyman, S Nurko, M Saps, C Di Lorenzo, RJ Shulman, JS Hyams, O Palsson, and MAL van Tilburg, 2018, Prevalence of Pediatric Functional Gastrointestinal Disorders Utilizing the Rome IV Criteria, J Pediatr, 195:134-139.
[5] https://theromefoundation.org/rome-iv/rome-iv-criteria/

- History of excessive stool retention
- History of painful or hard bowel movements
- History of large diameter stools
- Presence of a large fecal mass in the rectum

In toilet trained children, the following additional criteria may be used:

- At least one episode/week of incontinence after the acquisition of toileting skills
- History of large diameter stools which may obstruct the toilet

Source: Adapted from https://theromefoundation.org/rome-iv/rome-iv-criteria/
Section G7. Functional Constipation

The inclusion criteria for Study TAK-555-3010 required that subjects meet modified Rome IV criteria. For children/adolescents (aged >4 years) with FC, the modified Rome IV criteria required all subjects to meet the criterion of ≤2 defecations per week and 1 or more additional criteria from Rome IV, as listed in Table 1, occurring at least once per week for a minimum of 1 month. Similarly, for infants/toddlers (aged 6 months to ≤4 years) with FC, the modified Rome IV criteria required all subjects to meet the criterion of ≤2 defecations per week and 1 or more additional criteria from Rome IV, as listed in Table 2, occurring for at least 1 month. The original, unmodified Rome IV criteria did not assign priority to ≤2 defecations per week, but rather required subjects to experience two or more of any listed criteria.

2.2. Analysis of Current Treatment Options

In children, FC is usually initially treated with nonpharmacological therapy, which may include guidance on toileting behavior, physical activity, and dietary modifications (e.g., increasing fiber and fluid intake).

Linzess (linactotide) is the only FDA-approved pharmacologic treatment for pediatric patients with FC. On June 12, 2023, Linzess was approved for the treatment of FC in pediatric patients 6 to 17 years of age. Efficacy was not demonstrated for Amitiza (lubiprostone) for the treatment of FC in patients 6 years of age and older based on a 12 week, randomized, double-blind, placebo-controlled trial conducted in 606 patients 6 to 17 years with FC. Commonly used off-label treatments for chronic constipation in pediatric patients include nonprescription osmotic laxatives (e.g., polyethylene glycol, lactulose, magnesium citrate), stimulant laxatives (e.g., senna, bisacodyl), lubricant laxatives (e.g., mineral oil), and stool softeners (e.g., docusate, mineral oil).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Motegrity (prucalopride) was approved for the treatment of CIC in adults on December 14, 2018 (NDA 210166). Motegrity is supplied as 1 mg and 2 mg film-coated tablets. The recommended dosage for adults with CIC is 2 mg orally once daily.

The Applicant submitted a Prior Approval Supplement (PAS) on March 19, 2020, to update the prescribing information (PI) in the following two sections (NDA 210166/S-02).

- Section 5.1 *Suicidal Ideation and Behavior* to include cases from postmarketing experience.
- Section 8.1 *Pregnancy* to inform prescribers about the availability of a pregnancy exposure registry.

The Division of Gastroenterology (DG) consulted the Division of Pharmacovigilance I (DPV-I) on March 30, 2020, to evaluate if there have been additional reports of suicidal ideation and behavior (SIB) in the postmarketing setting since the time of product approval. The DPV team identified 8 cases of SIB/self-injurious behavior and 14 cases of new-onset or worsening of underlying psychiatric disorders (e.g., anxiety, depression, mood instability, nightmares, panic attacks, visual hallucinations). Based on review of these cases, the WARNINGS AND PRECAUTIONS section of prucalopride labeling was updated on November 9, 2020, to reflect the potential risk of SIB and self-injurious behavior in patients with and without a past medical history of psychiatric disease, and the *Postmarketing Experience* subsection was updated to list the following events: suicide, suicide attempts, suicidal ideation, self-injurious ideation, depression, anxiety, insomnia, nightmares, and visual hallucinations.

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 3 is a summary of the regulatory history of Motegrity specific to the pediatric development program.

Table 3: Key Regulatory Interactions for the Prucalopride Pediatric Chronic Idiopathic Constipation Program

Date/Activity	Description
December 18, 2018 Issuance of PREA PMRs	FDA issued PMR 3529-1 and 3529-2 at the time of NDA approval of Motegrity for treatment of CIC in adults.
May 24, 2019 Advice/Information Request	FDA issued advice on protocols SHP555-308 (proposed phase 3 confirmatory study; to support PMR 3529-1) and SHP555-309 (open label long-term safety study; to support PMR 3529-2). The Agency recommended revising the primary endpoint to evaluate the change in baseline in spontaneous bowel movement (SBM) frequency in comparison to the patient's baseline SBM frequency. The Agency also agreed with the Sponsor's proposal to change the design of the long-term safety trial from

Date/Activity	Description
	[redacted] (b) (4) to comparing two doses in a blinded design due to (1) anticipated recruitment challenges, and (2) therapies often used in clinical practice to treat pediatric patients with FC are a different route of administration and formulation as compared to prucalopride. Therefore, the blind would not be maintained and interpreting the comparative data would be difficult.
June 17, 2019 Advice/Information Request	The Agency agreed with the Sponsor's proposal to conduct the 12-week phase 3 confirmatory study and the 36-week extension study as one study, with a primary efficacy assessment at Week 12 and an interim analysis of efficacy and safety.
March 3, 2020 Advice/Information Request	The Agency provided advice on the protocol for TAK-555-3010 (combined SHP555-308 and SHP555-309 protocols) and statistical analysis plan (SAP), including recommendations on the variables to be included with the primary analysis model.
March 31, 2020 PREA PMR Release and Reissue	FDA released the Applicant from PMR 3529-2, reissued as PMR 3529-6 to reflect a design that evaluates two dose arms in a blinded study to assess long-term safety and tolerability.
September 15, 2020 Advice/Information Request	FDA conveyed disagreement with the Sponsor's proposal of [redacted] (b) (4) and the Agency recommended utilizing a composite estimand or a treatment policy estimand.
December 3, 2020 Advice/Information Request	FDA conveyed that the primary estimand population should be the same as the primary analysis population in TAK-555-3010.
November 10, 2021 Psychiatry review	The Division of Gastroenterology consulted the Division of Psychiatry (DP) to provide input on the TAK-555-3010 protocol to ensure that suicidal ideation/suicidal behavior (SI/SIB) are adequately monitored during the trial based on reports of SI/SIB in clinical trials and during post-approval use of prucalopride in adults. DP recommended: • Prospective assessments, specifically pediatric instruments or rating scales. • Additional safety monitoring and management plans.
January 21, 2022 Advice/Information Request	FDA provided recommendations regarding evaluation, monitoring, management, and reporting of SI/SIB during study TAK-555-3010, as outlined in the DP consult review.
May 26, 2022 Sponsor Response to Advice/Information Request	Sponsor's response to the January 21, 2022, FDA Advice/Information Request. The Sponsor proposed to forgo formal evaluation of SI/SIB at every visit (due to feasibility concerns and asking questions related to suicidal thoughts to subjects or parents might be triggering a "nocebo effect") and amend the TAK-555-3010 protocol to implement enhanced reporting of adverse events of special interest (AESI) and data monitoring committee (DMC) review of the data for SI/SIB in real time. The Agency notified the Applicant on July 22, 2022, via email that the proposal appeared reasonable.
November 21, 2022 Protocol TAK-555-3010 amendment 3	Protocol amendment to increased SI/SIB monitoring throughout the study based on the January 21, 2022, FDA Advice Letter, the Sponsor's response document dated May 26, 2022, and FDA's July 22, 2022, agreement of the proposal.
September 26, 2023 Type A Written Response	The Sponsor submitted a Type A Meeting Request on August 28, 2023, in which they informed the Agency of the independent DMC's recommendation to terminate of Study TAK-555-3010 for futility. FDA agreed with termination of Study TAK-555-3010 for futility, following review of the interim analysis and FDA's review of the operating characteristics of the interim futility analysis and simulation scenarios. The

Date/Activity	Description
	Agency recommended that the Applicant submit an efficacy supplement containing a complete study report with datasets, a proposed labeling update to the Prescribing Information, and a request to change the status of PMRs 3529-1 and 3529-6 to fulfilled.

Source: Reviewer generated tabled created from Applicant's submitted information in IND 055078 and NDA 210166

3.3. Additional Relevant History

A multicenter, randomized phase 3 study (SPD555-C303, ClinicalTrials.gov: NCT01330381) evaluating the efficacy and safety of prucalopride in children 6 months to 18 years with FC was conducted in Europe from April 2011 to March 2013. The complete safety and efficacy study results from this ex-US study were not submitted by the Applicant to FDA in the current supplement, but the information was used by the Applicant to inform the design of Study TAK-555-3010 and the pharmacokinetic data was used in population pharmacokinetic analysis (see Section 6 Clinical Pharmacology).

Study SPD555-C303 consisted of an 8-week double-blind, placebo-controlled period and a 16-week, open-label, active-controlled period. Subjects with FC, based on the Rome III criteria, received prucalopride (N=106, children ≤50 kg were given a 0.04 mg/kg oral solution; children >50 kg were given a 2 mg tablet) or placebo (N=107) once daily for 8 weeks. After 4 weeks of treatment, a weight-based dose adjustment to 0.06 mg/kg or 0.02 mg/kg could occur for subjects on the liquid formulation only, based on treatment response and the presence of safety or tolerability concerns, respectively. The primary efficacy endpoint was the proportion of responders in the last 4 weeks of the double-blind treatment period (Weeks 5 to 8). Responders were defined as subjects with a mean of ≥3 spontaneous bowel movements (SBMs) per week and ≤1 episode of fecal incontinence per 2 weeks (only for subjects after acquisition of toileting skills). The results showed that the proportion of responders was similar between treatment groups (prucalopride, 17.0% and placebo, 17.8%). The incidence of treatment-emergent adverse events was similar in the prucalopride (69.8%) and placebo (60.7%) groups.[6,7]

Study TAK-555-3010 was designed to potentially overcome some of the design issues with Study SPD555-C303 that may have contributed to the failure to demonstrate efficacy. The duration of Study TAK-555-3010 was 12 weeks (as compared to the duration of Study SPD555-C303 of 8 weeks) to provide a longer duration for bowel movement changes due to study drug. In addition, in Study TAK-555-3010, all subjects were required to undergo a fecal disimpaction procedure prior to randomization, and there was a standardized continuous behavioral therapy implemented for all subjects. Finally, the primary efficacy endpoint of Study TAK-555-3010

[6] Mugie SM, Korczowski B, Bodi P, Green A, Kerstens R, Ausma J, Ruth M, Levine A, Benninga MA. Prucalopride is no more effective than placebo for children with functional constipation. Gastroenterology. 2014 Dec;147(6):1285-95.e1. doi: 10.1053/j.gastro.2014.09.005. Epub 2014 Sep 16. PMID: 25239590.
[7] https://clinicaltrials.gov/study/NCT01330381?cond=NCT01330381&rank=1

differed from the primary efficacy endpoints of Study SPD555-C303 and the studies supporting the approval of Motegrity in the US for the treatment of CIC in adults which were based on responder definitions. During review of the draft protocol for Study TAK-555-3010, the Division recommended revising the primary endpoint from a responder definition to evaluate the change from baseline in SBM frequency, with the baseline used as a covariate in the analysis. This shift in thinking was based on feedback from sponsors, external experts, and ongoing discussions during which the Division questioned whether the responder definition which closely aligns with the endpoint used in the adult trials (i.e., a patient who had ≥ 3 SBMs and an increase of ≥ 1 SBM from baseline in a given week for at least 9 weeks out of the 12-week treatment period and for at least 3 of the last 4 weeks of the treatment period) would be applicable to pediatric patients.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The review team did not request clinical site inspections, as this study was terminated early for futility, an indication in pediatric patients for the treatment of FC is not requested by the Applicant, and the numeric study results will not be described in labeling.

4.2. Product Quality

The Applicant's request for Categorical Exclusion from the requirement of preparing and submitting an Environmental Assessment under 21 CFR 25.31(a) was found acceptable by OPQ and the supplement is recommended for approval. See review dated January 13, 2025, by Ramesh Gopalaswamy in Panorama.

4.3. Clinical Microbiology

Not applicable

4.4. Devices and Companion Diagnostic Issues

Not applicable

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Juvenile toxicology studies were conducted by the Applicant to support the safety of pediatric subjects aged 6 months to 17 years with FC in Study TAK-555-3010. The findings are briefly summarized in section 5.5 Toxicology below. Refer to the complete pharmacology/toxicology review by Sushanta Chakder, R.Ph., Ph.D., dated May 20, 2025, in DARRTS.

5.2. Referenced NDAs, BLAs, DMFs

Not applicable

5.3. Pharmacology

Not applicable

5.4. ADME/PK

Not applicable

5.5. Toxicology

A 28-day oral and a 49-day subcutaneous toxicity study was conducted in neonatal rats. The age of the animals used in the studies covers all pediatric age groups (i.e., newborn and older).

In the 28-day neonatal rat toxicity study with R108512 (Study #5002, (b) (4) , 15 male and 15 female neonatal Wistar rat pups/group were orally (gavage) administered prucalopride at dose levels of 5, 20 and 80 mg/kg/day. No test article-related mortality, clinical, ophthalmologic, gross pathological or histopathological observations were noted. In male and female pups dosed at 5 mg/kg/day, body weight and weight gain were slightly lower than controls. In male and female pups dosed at 20 mg/kg/day, body weight and weight gain were slightly decreased. In males, slight decreases in hematocrit, hemoglobin, white blood cells and lymphocytes were observed. In females, slight decreases in hematocrit and hemoglobin were observed. In male pups dosed at 80 mg/kg/day, body weight and weight gain were moderately decreased. In males, hematological examination revealed moderate decreases in hematocrits, hemoglobin, red blood cells, white blood cells and lymphocytes. Serum analysis in males showed a moderate increase in phospholipids and slight increases in chloride, cholesterol, and triglycerides, with no accompanied histopathological changes. Doses up to 80 mg/kg/day was tolerated well for 28 days in neonatal rats. The 5 mg/kg/day can be the NOAEL for males and 20 mg/kg/day can be the NOAEL for females based on ≥10% decrease body weight gain and changes in hematological parameters.

In the 49-day subcutaneous toxicity study ((b) (4) study number:CAJ0001, November 04, 2010) in neonatal rats (7 days old), three groups of animals (12/sex/group) received prucalopride at doses of 0 (vehicle), 2.5, 10 or 40 mg/kg/day from Day 7 to Day 55 of age, and an additional 20 male and 20 female rats were assigned to recovery groups followed by a 4-week period without treatment to assess reversibility of any treatment-related effect. All animals were assessed for clinical signs, body weight, food consumption, limb measurements, neurobehavioral examinations, hematology, blood chemistry, urinalysis, organ weight, macroscopic pathology, and histopathology investigations. There were no treatment related mortalities or toxicologically relevant clinical signs except a slightly increased incidence of scabs and thickening of the injection sites from Day 45 onwards in animals receiving the highest dose of 40 mg/kg/day. This effect was not observed at the end of the 4-week treatment-free recovery period.

Slightly lower body weight gains were observed in males receiving the 40 mg/kg/day dose and slightly higher weight gains and increased food consumption were observed in females. However, there were no effects on the length of limb (ulna) measurements. At 40 mg/kg/day, both males and females showed statistically significant delays in the average timing of sexual maturation. However, there was no reduction in body weight, and the timing of sexual maturation in individual animals was generally within the normal range. Neurological assessments did not show any abnormalities in either males or females. Learning ability and memory, assessed in the water-filled Morris maze, was unaffected by treatment.
White blood cell counts were slightly higher in males (more pronounced at 40 mg/kg), which were considered related to the inflammatory reactions at the subcutaneous injection sites. No treatment related changes in organ weights were observed at any dose level.

Macroscopic examinations revealed treatment related changes in the liver (extramedullary hemopoiesis) and at the injection sites (dermal/subdermal inflammation, epidermal hyperplasia, degeneration/inflammation, panniculus muscle, subcutaneous hemorrhage).

Thus, the NOAEL in this study was 10 mg/kg/day. The exposures of prucalopride in female pups were higher than that of males. The terminal half-life ranged from 3.1 to 6.3 hours on Day 7 of age, and 1.1 to 2.0 hours in males and 2.5 to 5.5 hours in females at Day 55 of age. The exposures (AUC) in male and female animals at 10 mg/kg/day at Day 55 of age were 2150 and 5310 ng.hr/mL, respectively. The C_{max} values in males and females were 874 and 1260 ng/mL, respectively.

There are no nonclinical findings to include in labeling.

6 Clinical Pharmacology

6.1. Executive Summary

Pharmacokinetic (PK) data from Study TAK-555-3010 along with PK data from two additional pediatric clinical studies of FC (Studies SPD555-303 and PRU-USA-12[8]) previously conducted in Europe and the US, respectively, were included by the Applicant in a population pharmacokinetic (PopPK) analysis to characterize the PK of prucalopride in pediatric subjects and evaluate the impact of covariates on the PK. No exposure-response analyses were conducted as the interim analysis of the primary endpoint in Study TAK-555-3010 indicated that the study was unlikely to demonstrate effectiveness and the study was terminated early for futility.

Briefly, Study TAK-555-3010 included a 12-week, placebo-controlled, double-blind part (Part A) followed by a 36-week long-term double-blind safety extension part (Part B) conducted in pediatric subjects aged 6 months to 17 years with FC.

Dosage regimens evaluated in Part A were as follows:

- Low dose: 0.04 mg/kg once daily (QD) if body weight (BW) <50 kg and 2 mg QD if BW ≥50 kg.
- High dose: 0.08 mg/kg QD if BW <50 kg and 4 mg QD if BW ≥50 kg.

The low and high dosage regimens were selected based on predicted exposure matching in children and adolescents with those of adults receiving 2 mg and 4 mg QD, respectively. Of note, both 2 mg and 4 mg QD were studied in phase 3 studies in adult patients with CIC; however, no additional clinical benefit was observed with the higher 4 mg QD dosage. In the Applicant's previous pediatric Study SPD555-303, evaluating prucalopride dosages ranging from 0.02 mg/kg to 0.06 mg/kg up to a maximum 2 mg QD, no efficacy was demonstrated. Therefore, the Applicant selected two dosage regimens in Study TAK-555-3010 that were projected to provide generally comparable exposure with those of adults receiving 2 mg QD and 4 mg QD.

Both prucalopride tablet (2 mg tablet, approved for adults with CIC) and oral solution (0.4 mg/mL) formulations were used in Study TAK-555-3010. Pediatric subjects weighing <50 kg (and those weighing ≥50 kg could not swallow tablets) received the oral solution while all others received the tablets.

[8] PRU-USA-12 was a single-dose (0.03 mg/kg, oral solution) pharmacokinetic study in pediatric subjects 4 years to <12 years with FC.

Key Clinical Pharmacology Review Findings:

- While the observed median concentrations of prucalopride in Study TAK-555-3010 appeared to be higher in the high dose group compared to those in the low dose group, the concentrations mostly overlapped between the two dose groups.
- PopPK analysis suggested similar PK characteristics across all pediatric studies. For the low dose, the predicted area under the plasma concentration-time curve at steady state (AUC_{ss}) and maximum plasma concentration at steady state ($C_{max,ss}$) in pediatric subjects were generally comparable to the exposures of adults receiving 2 mg QD. For high dose, the predicted AUC_{ss} and $C_{max,ss}$ were higher than in adults receiving 2 mg QD, but lower than the previously studied dosing regimen of 4 mg QD for 6 days in healthy adult subjects in the prucalopride development program.
- No labeling changes are proposed based on the PopPK analysis.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Summary of Clinical Pharmacology and Pharmacokinetics

Table 4: Summary of Clinical Pharmacology and Pharmacokinetics

Review Issue	Review Findings
Pharmacokinetics in adults	• Prucalopride exhibited dose-proportional PK in heathy subjects after repeated oral dosing of 1 to 20 mg QD. • T_{max} was observed within 2 to 3 hours after single oral dose of 2 mg with an absolute bioavailability >90%. • Following QD dosing, steady state was achieved within 3 to 4 days with an accumulation ratio ranging from 1.9 to 2.3. • No significant food effect was observed. • The terminal half-life was approximately 1 day. • The PK of prucalopride was similar between healthy subjects and patients with CIC.

Review Issue	Review Findings
Pharmacokinetics in pediatric subjects	• PopPK analysis suggested dose-proportional PK within the dose range evaluated in pediatric subjects aged 1 to 17.96 years. • Though observed plasma concentrations in high dose group of Study TAK-555-3010 was higher than that of low dose group, dose-adjusted concentration reversed the trend. This could be attributed to higher median body weight in the high dose group, very sparse sampling, and undetectable (below lower limit of quantitation) concentrations in a few subjects of high dose group. Model-predicted exposures also suggested a similar trend. • Predicted median AUC_{ss} and $C_{max,ss}$ between pediatric subjects (in Study TAK-555-3010 or pooled pediatric studies) in low dose group and adults receiving approved dose of 2 mg QD were comparable. However, predicted AUC_{ss} and $C_{max,ss}$ were higher in pediatric subjects in the high dose group compared to adults receiving 2 mg QD, but lower than the exposures associated with 4 mg QD in healthy adult subjects.
Impact of intrinsic and extrinsic factors on the PK	• Based on PopPK analysis, body weight was the most influential covariate on PK. Prucalopride clearance (CL) increased with increasing body weight. In pediatric subjects over a body weight range of 11 to 110 kg, prucalopride CL ranged from 5.42 to 30.5 L/hr, indicating that CL/F values ranged from 75% lower to 40% higher when compared to the typical value (21.7 L/hr) for a subject weighing 70 kg. • In both low and high dose groups, the median predicted steady state exposures (AUC_{ss} and $C_{max,ss}$) increased with increasing BW for weight-based dosing while the median predicted steady state exposures decreased with increasing BW for fixed dosing. • Other covariates such as age, sex, study (Phase 1 vs Phase 3), formulation, and estimated glomerular filtration rate (eGFR) had no impact on the prucalopride PK.
PK Bridging	• No dedicated PK-bridging study was conducted between the clinical solution and tablet formulations.

Source: created by the reviewer

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Clinical Pharmacokinetics

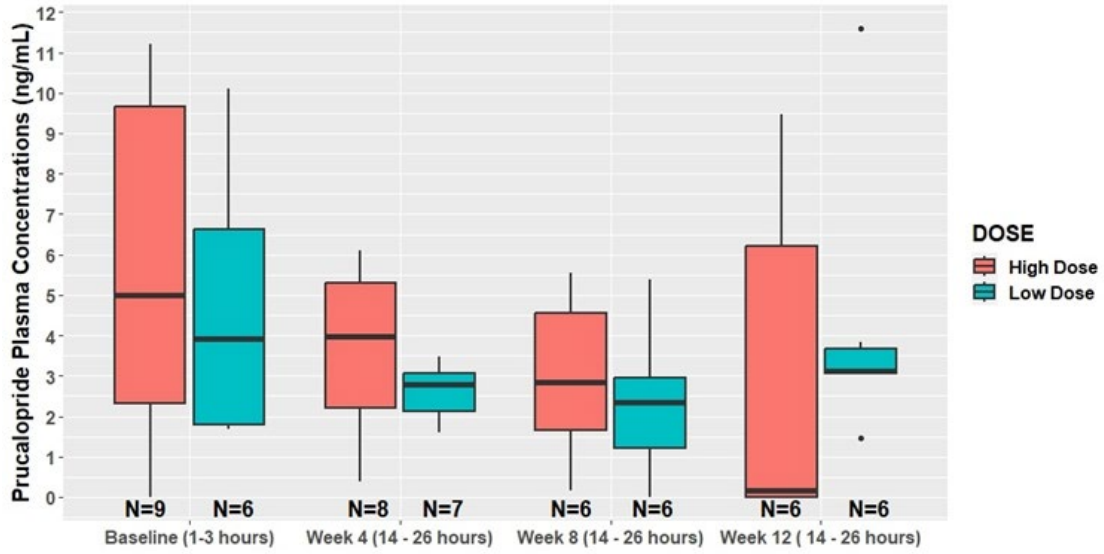
Prucalopride is a serotonin type 4 ($5\text{-}HT_4$) receptor agonist. It acts as a GI prokinetic agent that stimulates colonic peristalsis and accelerates colonic transit.

Pharmacokinetic (PK) data from Study TAK-555-3010 along with PK data from two additional pediatric studies (Studies SPD555-303 and PRU-USA-12) were submitted to allow for a PopPK analysis that aided in the PK characterization of prucalopride in pediatric subjects with FC. Additionally, the impact of intrinsic/extrinsic factors on the PK were evaluated, and model-predicted exposures were generated to allow for comparison between pediatric subjects and adults with CIC.

Pharmacokinetics of prucalopride in pediatric subjects with functional constipation

In Study TAK-555-3010, the observed plasma concentrations of prucalopride from baseline to Week 8 appeared to be generally higher in the high dose group but largely overlapped with those of the low dose group (Figure 1). Of note, the median plasma concentration of the high dose group at Week 12 was 0.17 ng/mL, which was lower than that of the low dose group (3.12 ng/mL). This is likely because the concentrations were below lower limit of quantification (LLOQ) in 3 out of 6 subjects of the high dose group. The reason for largely overlapping concentrations in the high and low dose groups is not clear but may be attributed to the sparse PK sampling in a limited number of subjects, as well as a higher median body weight and several undetectable plasma concentrations observed in the high dose group.

Figure 1: Plasma Concentrations-Time Profile of Prucalopride Stratified by Dose Group for Study TAK-555-3010

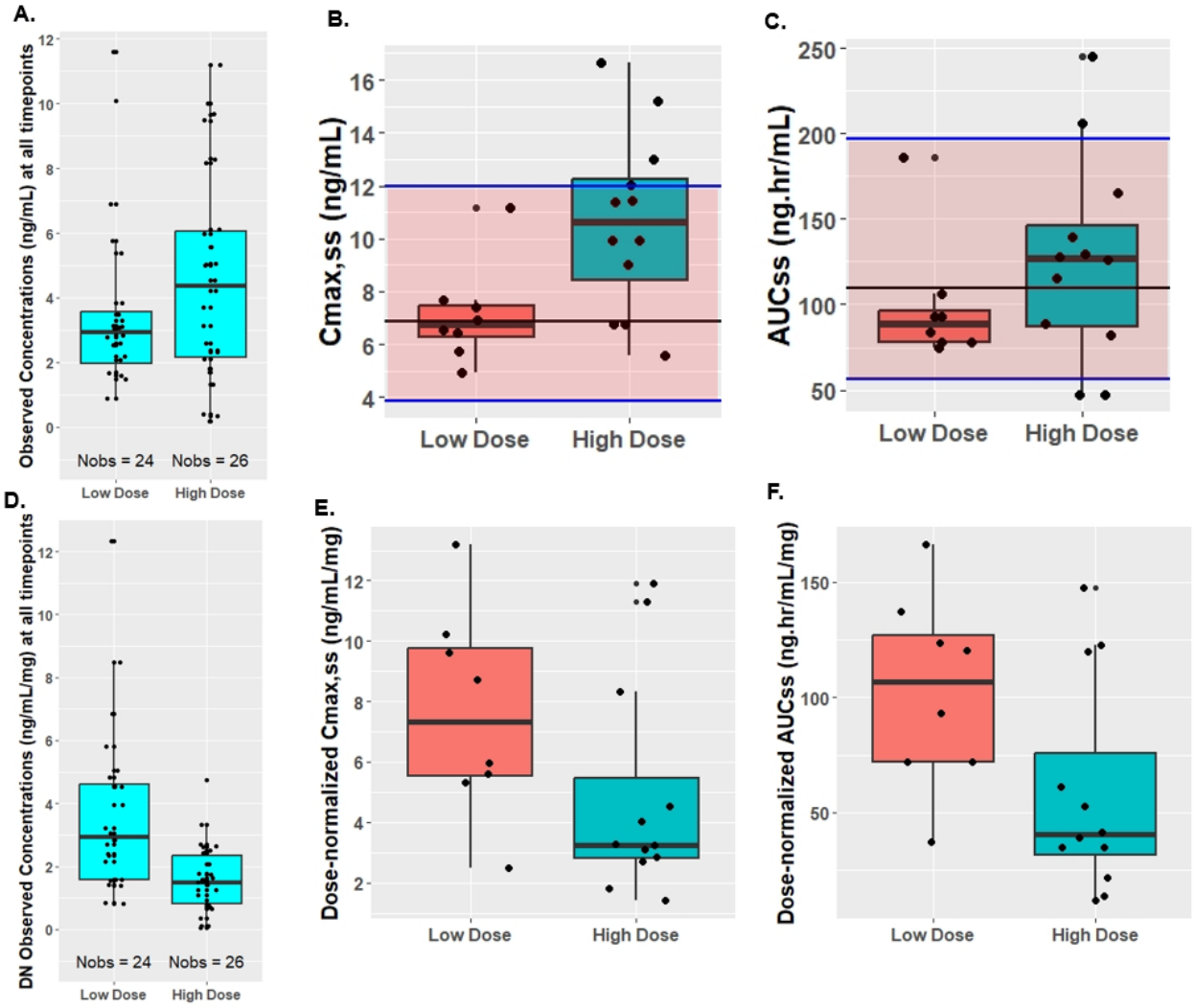


Source: Reviewer analysis based on the data from Study TAK-555-3010

Pooled plasma concentrations of TAK-555-3010 also showed that high dose tended to have higher concentrations, albeit largely overlapped with low dose concentrations which is also supported by predicted $C_{max,ss}$ and AUC_{ss} (Figure 2A-C). However, the dose-normalized median concentration in the high dose group is lower than that of the low dose group, implying less than dose-proportional PK in this study. While this phenomenon is also supported by predicted exposures (Figure 2D-F), the data should be interpreted with caution given the very sparse

sampling and undetectable concentrations in several subjects in high dose group. PopPK analysis conducted using pooled pediatric studies suggested dose-proportional PK based on the 90% prediction interval of dose-normalized, model-predicted $C_{max,ss}$ and AUC_{ss}. The model-predicted dose-normalized $C_{max,ss}$ and AUC_{ss} were also consistent across all pediatric studies, implying no impact of study on the PK (See section 14.4.2 Population Pharmacokinetic Analysis).

Figure 2: Observed and Predicted PK Exposures for Study TAK-555-3010



Source: Reviewer's analysis based on data from Stud TAK-555-3010 and final PopPK model
DN: Dose-normalized. **A and D**: Plasma concentrations are pooled from all time points. **B and C**: Predicted exposures based on post-hoc PK parameters; Pink shaded area: adult 90% prediction interval for $C_{max,ss}$ (4 – 12 ng/mL) and AUC_{ss} (57 – 197 ng.hr/mL). Median $C_{max,ss}$ and AUCss are 6.86 ng/mL and 109.3 ng.hr/mL. **E and F**: Dose-normalized predicted exposures based on post-hoc PK parameters

Simulation was performed using the final PopPK model to generate AUC_{ss} and $C_{max,ss}$ based on individual post-hoc PK parameters in all pediatric studies. Predicted $C_{max,ss}$ and AUC_{ss} in the low

dose group in Study TAK-555-3010 were comparable with those of adults receiving the approved dosage regimen for CIC of 2 mg QD. However, exposures are higher in the high dose group than in adults who received 2 mg QD. Nevertheless, the steady state exposures in the high dose group do not exceed those observed in healthy adult subjects receiving 4 mg QD for 6 days (Table 5).

Table 5: Simulated Exposures of Prucalopride at Steady-State in Pediatrics and Reference Exposures in Adults

	TAK-555-3010[a]		Pooled pediatric population[b]		Reference population	
PK parameters	Low dose (N=8)	High dose (N=12)	Low dose (N=195)	High dose (N=195)	Adult 2 mg QD[c] (N=1343)	Adult 4 mg QD[d] (N=12)
AUCss (ng.h/mL)	93.2 (78.8 – 159)	153 (47.8 – 225)	87.7 (54.5 – 126)	175 (109 – 253)	109.3 (56.6 – 197.1)	219 (38)
Cmax,ss (ng/mL)	6.74 (5.7 – 10)	11.5 (6.29 – 15.9)	6.73 (4.78 – 8.49)	13.5 (9.56 – 17)	6.86 (3.86 – 11.96)	15.2 (2.6)

Source: m2.5-seq0506 – Clinical Overview Addendum, table 3a updated with PK study results from Study PRU-BEL-15
AUCss: area under the plasma concentration-time curve at steady-state; Cmax,ss: maximum observed plasma concentration at steady-state. Simulated PK parameters include median (90% prediction interval) except for Adult 4 mg QD. For Adult 4 mg QD, mean (SD) has been reported.
[a] PopPK Posthoc PK parameters from the PopPK modeling report
[b] Data from pediatric studies TAK-555-3010, SPD555-303, and PRU-USA-12; PopPK simulation with TAK-555-3010 dosing regimen
[c] Data from 13 studies in adult participants (phases 1, 2, and 3)
[d] Data from Study PRU-BEL-15 that evaluated 4 mg QD for 6 days. Mean (SD) PK parameters are reported

No exposure-response analysis was conducted after Study TAK-555-3010 was terminated early prior to full enrollment. Per the Applicant's interim analysis, there was no meaningful difference in the change of efficacy endpoints from baseline between placebo and low dose or high dose groups.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 6 is an overview of the single phase 3 clinical trial (Study TAK-555-3010) to assess the safety and efficacy of prucalopride in pediatric subjects 6 months to 17 years of age with FC.

Table 6: Overview of Study TAK-555-3010

Study Number	Trial Design	Oral Once Daily Dosing Regimen	Endpoints	Duration	Sample Size	Study Population	Centers and Countries
TAK-555-3010	Phase 3, multicenter, randomized study consisting of a 12-week double-blind, placebo-controlled part (Part A) followed by a 36-week double-blind safety extension part (Part B).	Low Dose: 2 mg prucalopride *weighing <50 kg 0.04 mg/kg prucalopride, weighing ≥50 kg* High Dose: 4 mg prucalopride *weighing <50 kg 0.08 mg/kg prucalopride, weighing ≥50 kg* Or matching placebo (Part A only)	Primary endpoint (in toilet-trained subjects who were at least 3 years of age): Average change from baseline in number of SBMs per week over 12 weeks (Part A).	Screening: 10 to 33 days Placebo-controlled part (Part A): 12 weeks Safety extension (Part B): 36 weeks Follow-up: 4 weeks	175 subjects	Toilet-trained subjects 3 to 17 years of age, inclusive, or non-toilet-trained subjects 6 months to 17 years of age, inclusive, with FC.	24 study sites in the United States

Source: created by the reviewer

7.2. Review Strategy

Review of efficacy and safety was based on data from a single phase 3, multicenter, randomized study in pediatric subjects 6 months to 17 years of age with FC.

Study TAK-555-3010 consisted of a 12-week double-blind, placebo-controlled part (Part A) followed by a 36-week double-blind safety extension part (Part B) in pediatric subjects with FC. After completion of Part A, subjects in the placebo group were rerandomized in a 1:1 ratio to the low-dose or high-dose groups (Part B). Approximately 240 toilet-trained subjects, 3 to 17 years of age with FC, were planned for randomization in a 1:1:1 ratio to the low-dose, high-dose, or matching placebo groups (Part A). For exploratory purposes, in addition to the 240 toilet-trained pediatric subjects, the study planned to enroll a maximum of 15 subjects who were not toilet trained and at least 6 months of age. These subjects were not to be included in the primary analyses given that the instruments used to evaluate the efficacy parameters had not been considered fit-for-purpose in participants <3 years of age and it may be difficult to quantify BMs from diapers. The non-toilet-trained group was analyzed separately from the toilet-trained group, by the Applicant and the review team, , but the limited sample size precluded any efficacy conclusions.

Per protocol, when approximately 50% of toilet-trained subjects (i.e., 120 subjects) were randomized into the study and had completed Part A, an interim analysis (IA) was performed to compare the efficacy of both prucalopride doses with placebo. The main purpose of the IA was to decide to continue or stop the study for futility. The protocol specified that the futility evaluation would be based on the conditional power using a stopping threshold of 20% for each dose arm.

An independent data monitoring committee (DMC) reviewed the unblinded IA results and recommended that the study be terminated for futility on August 21, 2023. As detailed in the Type A written responses, dated September 26, 2023, based on the results of the IA and results from simulations evaluating the operating characteristics of the IA, the FDA agreed with the Applicant that it was reasonable to terminate the study early for futility.

The review team also reviewed the results of the interim analysis for the primary endpoint and the simulations performed by the Applicant to evaluate the operating characteristics of the interim analysis. The team also concluded the study met the criteria for futility (i.e., conditional power <20% for each dose) and that if continued after meeting the futility criteria, the trial was unlikely to demonstrate superiority.

In SAP Version 5, dated November 24, 2023, and submitted after the Applicant had performed the IA, the Applicant added language indicating that no inferential analyses of efficacy would be performed if the study was terminated early for efficacy. Primary, secondary, and exploratory endpoints would only be reported in a descriptive manner. Therefore, the review team started

by assessing these descriptive results and considered whether additional inferential analyses would also be needed from the Applicant.

After reviewing the reported results and performing the prespecified primary analysis of the primary endpoint, the review team concluded that for this application, the descriptive results provided an adequate overall summary of treatment efficacy and were sufficient for the purposes of describing the failed study in labeling.

For safety, in addition to reviewing the adverse events reported in pediatric subjects in Study TAK-555-3010 and assessing any reports of suicidal ideation/suicidal ideation and behavior (SI/SIB) as adverse events of special interest (AESIs), the pediatric safety data were also reviewed in the context of the known safety profile of prucalopride in adults with CIC. DPV conducted a review of postmarketing reports of unlabeled psychiatric adverse events and serotonin syndrome since initial approval.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study TAK-555-3010, 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

Trial Design

The study included a 10 to 33-day screening period, including a disimpaction for all subjects, a 12-week, double-blind, placebo-controlled part (Part A) followed by a 36-week, long-term double-blind (for dose) safety extension part (Part B), and a follow-up call approximately 4 weeks after the last administration of the study drug. Approximately 240 toilet-trained subjects 3 to 17 years of age with functional constipation, as defined by the modified Rome IV criteria for child/adolescent functional gastrointestinal disorders (FGID), were planned for randomization in a 1:1:1 ratio to the low-dose group, high-dose group, or matching placebo (Part A). After completion of Part A, participants in the placebo group were rerandomized in a 1:1 ratio to the low-dose group or the high-dose group (Part B).

In addition to the 240 toilet-trained pediatric subjects, a maximum of 15 subjects who were not toilet trained and at least 6 months of age were to be enrolled in the study for exploratory purposes. These subjects were not included in the primary analyses.

Dosing Regimen
Both in Part A and Part B of the study, subjects in the low-dose group weighing <50 kg at the randomization visit received a dosage of 0.04 mg/kg prucalopride once daily, and subjects weighing ≥50 kg received a dosage of 2 mg prucalopride once daily. Subjects in the high-dose group weighing <50 kg at the randomization visit received a dosage of 0.08 mg/kg prucalopride once daily, and subjects weighing ≥50 kg received a dosage of 4 mg prucalopride once daily.

Electronic Diary (e-Diary)
There were 3 versions of the e-Diary:

- Self-completed for toilet-trained participants ≥8 years of age
- Caregiver completed for toilet-trained participants ≥3 but <8 years of age, with participant input, as appropriate
- Caregiver completed for non-toilet-trained participants ≥6 months of age

Efficacy was assessed based on variables recorded in the e-Diary. During Part A for toilet-trained subjects, e-Diary items recorded for each bowel movement (BM) included the date and time of the BM, consistency (using the Bristol Stool Form Scale with scores ranging from 1 [indicative of constipation] to 7 [indicative of diarrhea]), level of straining needed (using a 3-level Likert Scale where 1 is "not at all," 2 is "a little," 3 is "a lot"), and worst abdominal pain (using Wong-Baker self-assessment faces scale for participants ≥3 to <8 years of age and the 11-point numerical response scale where 0 is "no pain" and 10 is the "worst pain imaginable" for participants ≥8 years of age).

Study Endpoints

The SAP defines the primary endpoint as "[t]he average change from baseline (CFB) in number of spontaneous bowel movements (SBMs[9]) per week derived from the (diary) data over 12 weeks, collected during the placebo-controlled part (Part A)". Based on this statement, the primary endpoint was defined by the reviewers to be the CFB in SBM per week averaged over 12 weeks (e.g., the average of 12 weekly values) in this review.

The three key secondary endpoints are:

1) The average change from baseline in stool consistency (based on Bristol Stool Form Scale [BSFS] score), assessed as the weekly average during the 12-week double-blind, placebo-controlled treatment phase. Summaries will be reported separately for subjects aged <8 years and 8 to 17 years based on reporter status (parent/child).

2) The average change from baseline in straining (based on a 3-point Likert scale), assessed as the weekly average during the 12-week double-blind, placebo-controlled treatment

[9] A bowel movement (BM) is defined as spontaneous (SBM) if not preceded within a period of 24 hours by the intake of rescue medication or within 24 hours after disimpaction period.

phase.

3) The proportion of responders with a responder defined as a subject having an increase of ≥1 SBM/week compared to baseline and ≥3 SBMs/week for at least 9 out of the 12 weeks of placebo-controlled part (Part A), including 3 of the last 4 weeks.

Statistical Analysis Plan

Analysis Populations

For Part A, the Intent to Treat (ITT) Analysis Set includes all randomized subjects, and both the modified Intent to Treat (mITT) Analysis Set and the Safety Analysis Set includes all randomized subjects who receive at least 1 dose of investigational product in Part A. The treatment arm will be the arm to which they were randomized, regardless of what treatment they received.

Interim Analysis (IA)

The primary objective of the IA was to evaluate whether the study should be stopped for futility. The IA was conducted when 50% of target number of toilet-trained subjects who are at least 3 years of age (i.e., 120 subjects) were randomized into the study and either completed or had withdrawn from the placebo-controlled part (Part A). Futility evaluation was based on the conditional power[10] using a stopping threshold of 20% for each dose arm. If both comparisons, low dose and high dose versus placebo, had a conditional power (probability) of less than 20%, the study would be stopped for futility.

Calculation of the Primary Endpoint

The average number of SBM in study week *j* was calculated as follows:

Number of SBM in Week *j* = 7 x (total frequency of SBMs in Week *j*)/(# days with observations in Week *j*).

For the calculation of the number of weekly SBM, at least 4 days with completed diary data (i.e., evaluable days) were required; otherwise, the number of weekly SBM was set to missing. A day was considered evaluable (day with diary information) if at least some information on BM was recorded (i.e., 'no BM today' or the time of at least 1 BM was recorded).

The average number of SBM per week in the screening period was defined similarly.

[10] Lan, K. K. and Wittes, J. 1988. The B-value: a tool for monitoring data. *Biometrics,* 44(2), 579-85.

Primary Efficacy Analysis of the Primary Endpoint

The following analysis was prespecified as the final analysis in the SAP. See Section 7.2 Review Strategy for a discussion on the completion of this analysis given that the study was terminated early for futility.

The primary analysis of the primary efficacy endpoint would have used a Mixed Model with Repeat Measurements (MMRM) based on Restricted Maximum Likelihood (REML). The fixed effects would include treatment, age group (< 12, 12-17 years), baseline average weekly SBM, study week, and treatment-by-study-week interaction. Within-subject variability would be modeled by an unstructured covariance matrix. The average change from baseline over 12 weeks would be estimated (LS means) and the treatment difference in LS means between each active treatment group and the placebo group would also be estimated.

Missing data would be imputed using a hybrid imputation approach. Subjects who discontinued due to lack of efficacy or AE would be imputed using the worst observation carried forward (WOCF). All other missingness would be imputed using multiple imputation under the missing at random (MAR) assumption. For multiple imputation, the weekly number of SBMs would be imputed by treatment group using a regression model that includes previous weeks' SBM measures and a predictive mean matching method with the number of donor observations set to 5. Twenty multiply imputed datasets would be generated. The MMRM would be applied to each of the twenty datasets and results will be combined using Rubin's rules.

The primary efficacy analysis would be based on the mITT for toilet trained subjects who are at least 3 years of age.

Protocol Amendments

The final version of protocol TAK-555-3010 was dated October 21, 2020. The primary purpose for protocol amendment 1, dated December 18, 2020, was to incorporate the comments and recommendations from the FDA communicated in an Advice Letter, dated December 3, 2020. The Advice Letter focused on revising the primary endpoint for clarity to specify the timing of the primary efficacy assessment and proposed COVID-19 specific measures, as well as comments and recommendations from clinical outcome assessment and statistical teams.

The primary reasons for protocol amendment 2, dated October 20, 2021, was to provide the option to switch to oral solution for subjects weighing ≥50 kg who cannot tolerate the tablets, align the screening window throughout the protocol, and clarify how rescue medication will be obtained.

The primary purpose for protocol amendment 3, dated October 27, 2022, was to incorporate comments and recommendations from the FDA communicated in an Advice Letter, dated January 21, 2022. The Advice Letter focused on monitoring for suicidal ideation and behavior (SIB) and including SIB as an AESI.

8.1.2. Study Results

Compliance with Good Clinical Practices

This study was performed in accordance with Good Clinical Practice regulations and guidelines.

Financial Disclosure

The Applicant submitted adequate financial disclosures regarding the clinical investigators for Study TAK-555-3010 (see 14.2 Financial Disclosure). The review team did not identify any concerns from any of the financial disclosures.

Patient Disposition

Subject disposition for Part A is summarized in Table 7. Of the 175 subjects in the safety population, 134 subjects (76.6%) completed Part A and 41 subjects (23.4%) discontinued study drug and study. The most common reason for study drug and study discontinuation was withdrawal of consent (17 subjects, 9.7%). A larger percentage of subjects in the high dose group (33.9%) discontinued the study drug and study, as compared to subjects in the low dose group (18.3%) and placebo group (17.9%). The higher proportion of study drug and study discontinuation in the high dose group was primarily due to withdrawal of consent by subject and loss to follow-up. This imbalance regarding premature study drug or study discontinuations among treatment groups was unlikely to significantly affect the study outcome or interpretation of results.

Table 7: Disposition by Treatment Group (Part A) (Safety Analysis Set)

	Placebo N=56	Prucalopride Low Dose N=60	Prucalopride High Dose N=59	Total N=175
Discontinuation from treatment	10 (17.9)	11 (18.3)	20 (33.9)	41 (23.4)
Adverse event	1 (1.8)	5 (8.3)	2 (3.4)	8 (4.6)
Loss to follow-up	4 (7.1)	1 (1.7)	4 (6.8)	9 (5.1)
Noncompliance with study drug	0	0	1 (1.7)	1 (<1)
Physician decision	0	0	1 (1.7)	1 (<1)
Study terminated by sponsor	0	2 (3.3)	3 (5.1)	5 (2.9)
Withdrawal of consent by subject	5 (8.9)	3 (5.0)	9 (15.3)	17 (9.7)
Discontinuation from study	10 (17.9)	11 (18.3)	20 (33.9)	41 (23.4)
Adverse event	1 (1.8)	4 (6.7)	2 (3.4)	7 (4.0)
Lack of efficacy	0	0	1 (1.7)	1 (<1)
Loss to follow-up	4 (7.1)	1 (1.7)	4 (6.8)	9 (5.1)
Noncompliance with study drug	0	0	1 (1.7)	1 (<1)
Physician decision	0	1 (1.7)	0	1 (<1)
Study terminated by sponsor	0	2 (3.3)	3 (5.1)	5 (2.9)
Withdrawal of consent by subject	5 (8.9)	3 (5.0)	9 (15.3)	17 (9.7)

Source: Clinical Study Report Table 10.b (page 80). Verified by reviewer using ADSL.xpt.
Abbreviations: N=number of subjects in population treatment group

Protocol Violations/Deviations

Table 8 shows protocol deviations in the Screening and Part A periods of Study TAK-555-3010 by treatment group. The distribution of major protocol deviations was similar among the study sites. Major protocol deviations were reported for approximately 25% of subjects in all groups and were mostly related to poor e-Diary compliance.

Three subjects reported critical protocol deviations.

- Two subjects (high dose, placebo) experienced medication dispensing errors, and were dispensed medication without recording the medication into the appropriate system. The errors were realized 2 days later, and the subjects' caregivers returned the study drug to the site. The caregivers reported no TEAEs related to the incident.
- One subject (low dose) signed the youth assent form, but the subject's parents did not sign the parent ICF.

Table 8: Protocol Deviations by Classification – Screening and Part A (Safety Analysis Set)

Protocol deviation	Placebo N=56	Prucalopride Low Dose N=60	Prucalopride High Dose N=59	Total N = 175
Subjects with at least 1 significant protocol deviation, n (%)				
Minor	43 (76.8)	47 (78.3)	41 (69.5)	131 (74.9)
Major	13 (23.2)	13 (21.7)	17 (28.8)	43 (24.6)
Critical	1 (1.8)	1 (1.7)	1 (1.7)	3 (1.7)

Source: Base on Clinical Study Report Table 10.e (page 82). Generated by reviewer using ADSL.xpt, DV.xpt, and SUPPDV.xpt.
Abbreviations: N=number of subjects in population treatment group

Demographic and Baseline Disease Characteristics

Subject demographics for the Part A Safety population are summarized in Table 9. The majority of subjects were female (52.0%), White (57.1%), and between 3 and 12 years old (60.6%). Among the 175 subjects, 163 subjects (93.1%) were toilet trained and at least three years of age. Demographic characteristics were generally similar among treatment groups. However, the percentage of male subjects was slightly higher in the high dose group (52.5%) and low dose group (53.3%), as compared to the placebo group (37.5%). The small differences in sex and ethnicity among treatment groups are unlikely to significantly impact the overall conclusions of the study.

Table 9: Demographic Characteristics by Treatment Group (Part A) (Safety Analysis Set)

	Placebo N=56	Prucalopride Low Dose N=60	Prucalopride High Dose N=59	Total N=175
Age group, n (%)				
6 months to < 3 years	1 (1.8)	3 (5.0)	2 (3.4)	6 (3.4)
≥ 3 years to < 12 years	35 (62.5)	35 (58.3)	36 (61.0)	106 (60.6)
≥ 12 years	20 (35.7)	22 (36.7)	21 (35.6)	63 (36.0)
Age, years				
Mean (SD)	9.4 (3.7)	9.8 (4.0)	9.8 (4.0)	9.7 (3.9)
Median	9.5	10.0	10.0	10.0
IQR	7.0, 12.0	7.0, 13.0	7.0, 13.0	7.0, 13.0
Min, Max	2, 16	2, 17	1, 17	1, 17
Sex, n (%)				
Female	35 (62.5)	28 (46.7)	28 (47.5)	91 (52.0)
Male	21 (37.5)	32 (53.3)	31 (52.5)	84 (48.0)
Toilet trained[a], n (%)				
Toilet-trained	52 (92.9)	56 (93.3)	55 (93.2)	163 (93.1)
Non-toilet-trained	4 (7.1)	4 (6.7)	4 (6.8)	12 (6.9)
Race, n (%)				
American Indian or Alaska Native	0	1 (1.7)	1 (1.7)	2 (1.1)
Asian	0	0	0	0
Black or African American	23 (41.1)	22 (36.7)	23 (39.0)	68 (38.9)
Native Hawaiian	0	0	0	0
White	31 (55.4)	34 (56.7)	35 (59.3)	100 (57.1)
Not Reported	2 (3.6)	1 (1.7)	0	3 (1.7)
Multiple	0	2 (3.3)	0	2 (1.1)
Ethnicity, n (%)				
Hispanic or Latino	23 (41.1)	28 (46.7)	30 (50.8)	81 (46.3)
Not Hispanic or Latino	33 (58.9)	32 (53.3)	29 (49.2)	94 (53.7)
Not Reported	0	0	0	0
BMI (kg)				
Mean (SD)	20.8 (6.7)	21.6 (6.5)	20.4 (6.3)	20.9 (6.5)
Median	17.7	20.4	18.6	19.0
IQR	16.0, 23.3	16.5, 25.7	15.7, 24.1	16.1, 24.1
Min, Max	14, 41	10, 40	13, 49	10, 49
Time since diagnosis[b] (years)				
Mean (SD)	3.2 (2.9)	4.2 (3.7)	4.0 (3.8)	3.8 (3.5)
Median	1.9	2.6	2.9	2.5
IQR	1.2, 4.4	1.6, 6.5	1.4, 5.6	1.4, 5.5
Min, Max	0, 12	0, 16	0, 17	0, 17
Missing	1	2	0	3

Source: Clinical Study Report Table 11.d (page 85). Verified by reviewer using ADSL.xpt.

[a] Toilet-trained subjects include all subjects who were at least 3 years of age. Non-toilet-trained participants included subjects between 6 months and 3 years of age.

[b] Time since diagnosis of constipation was calculated as treatment start date minus date of constipation diagnosis plus one.

Abbreviations: BMI=body mass index; max=maximum; min=minimum; N=number of subjects in population treatment group; n=number of subjects in subgroups; SD=standard deviation.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance for Part A is summarized in Table 10. Treatment compliance was calculated by the number of days treatment was reported to be taken divided by the duration of exposure. The mean treatment compliance was 70.6% and was similar across all treatment groups in Part A. An IR was sent to the Applicant on December 11, 2024, to provide rationale as to why the mean compliance with study drug intake was approximately 70%. The Applicant responded on January 10, 2025, and stated that based on the information collected from the diary, it was not possible to distinguish noncompliance from missing data. Therefore, the reported compliance may be influenced by both a subject's failure to report taking treatment and/or the actual failure to take a treatment. Additional contributing factors to low compliance with study drug intake may include treatment emergent AEs or lack of efficacy.

To evaluate the potential impact of compliance on estimates of efficacy, exploratory analyses evaluated results within improper subgroups defined by levels of compliance. The overall conclusions (e.g., lack of efficacy) were consistent across "subgroups" defined by compliance, suggesting that low compliance was not the primary cause of the lack of observed efficacy. The results of these exploratory analyses should be interpretated with caution as this is not a randomized comparison and subjects belonging to each "subgroup" may differ across arms.

Table 10: Study Drug Exposure and Compliance (Part A) (Safety Analysis Set)

	Placebo N=56	Prucalopride Low Dose N=60	Prucalopride High Dose N=59	Total N=175
Percent compliance[a]				
Mean (SD)	73.8 (20.0)	73.2 (21.7)	67.9 (24.7)	71.6 (22.3)
Median	79.3	78.4	76.1	78.1
IQR	66.7, 87.5	63.1, 90.7	48.8, 85.7	61.9, 87.6
Min, Max	2, 99	6, 100	2, 100	2, 100
Missing	1	1	1	3
Compliance[a], n (%)				
<60%	9 (16.1)	12 (20.0)	19 (32.2)	40 (22.9)
60%-85%	28 (50.0)	26 (43.3)	22 (37.3)	76 (43.4)
>85%	18 (32.1)	21 (35.0)	17 (28.8)	56 (32.0)
Missing	1 (1.8)	1 (1.7)	1 (1.7)	3 (1.7)

Source: Clinical Study Report Table 11.g (page 90). Verified by reviewer using ADQS.xpt.
a Compliance was calculated as the number of days treatment was taken (based on self-reported diary data) divided by duration of exposure.
Abbreviations: max=maximum; min=minimum; N=number of subjects in population treatment group; SD=standard deviation

Efficacy Results – Interim Analysis

The results of the interim analysis are summarized in Table 11. The mean CFB in SBM per week averaged over 12 weeks and averaged across 20 imputations was 1.76 in the placebo group, 2.13 in the low dose group, and 1.11 in the high dose group. Based on these results, the

estimated conditional power to demonstrate superiority was 11.58% in the low dose group and < 0.01% in the high dose group. Therefore, the study met the criteria for futility (i.e., conditional power <20% for each dose) and the study was terminated early.

Table 11: Conditional Power (Part A: Toilet-Trained Participants who were at Least 3 Years of Age) (Modified Intent-to-Treat Analysis Set)

	Placebo N=38	Prucalopride Low Dose N=41	Prucalopride High Dose N=41
CFB in SBM per week, Mean[a,b] (SD)	1.76 (1.86)	2.13 (2.29)	1.11 (1.17)
Z-statistic[a]		0.78	-1.86
Conditional Power[c]		11.58%	<0.01%

Source: Based on Clinical Study Report Table 11.j (page 90). Verified by reviewer using ADIMP.xpt
[a] Mean (SD) CFB in SBM per week averaged over 12 weeks and Z-statistic are averages based on 20 imputed datasets.
[b] All BM were considered SBM for the one subject who took all rescue medication "as needed" without providing specific dates.
[c] Conditional power was calculated based on the B-value as described by Lan and Wittes[11]
Abbreviations: N=number of subjects in population treatment group; SD=standard deviation

Efficacy Results – Primary Endpoint

The descriptive results for the CFB in SBM endpoint at Week 12 are summarized in Table 12. The results are based on the 163 subjects randomized into Part A. The mean (SD) CFB in SBM per week at Week 12 was 2.1 (2.80) in the placebo group, 2.1 (2.53) in the low dose group, and 1.1 (1.59) in the high dose group. Therefore, the mean CFB in SBM was no larger in the active treatment groups, as compared to the placebo group, and the treatment does not appear to significantly increase the CFB in SBM. Conclusions were similar in subgroups defined by age, number of SBM at baseline, and compliance levels (Table 33), and throughout the 12 weeks of the trial (Figure 7).

[11] Lan, K. K. and Wittes, J. 1988. The B-value: a tool for monitoring data. *Biometrics,* 44(2), 579-85.

Table 12: Change from Baseline in Average Number of Weekly SBMs at Week 12 (Part A: Toilet-Trained Participants who were at Least 3 Years of Age) (Modified Intent-to-treat Analysis Set)

	Placebo N=52		Prucalopride Low Dose N=56		Prucalopride High Dose N=55	
	Observed value	Change from baseline	Observed value	Change from baseline	Observed value	Change from baseline
Week 12						
n	41	41	44	44	38	38
n*	36	36	30	30	28	28
Mean[a] (SD)	3.4 (2.7)	2.1 (2.8)	3.6 (2.3)	2.1 (2.5)	2.5 (1.5)	1.1 (1.6)
Median[a]	2.6	1.3	3.0	1.6	2.0	0.5

Source: Clinical Study Report Table 11.l (page 96). Verified by reviewer using ADBOWEL.xpt
[a] Mean (SD) and median were based on subjects with non-missing measurements
Abbreviations: N=number of subjects in population treatment group; n=number of subjects with at least 1 assessment during Week 12; n*=number of subjects with a non-missing measurement (i.e., ≥ 4 assessments during Week 12 and the screening period); SBM=spontaneous bowel movement; SD=standard deviation

The FDA reviewers performed the analysis that was prespecified as the primary analysis for the primary endpoint in the SAP. The FDA reviewers evaluated the average CFB in number of weekly SBMs over the 12 weeks in Part A using the MMRM prespecified in the SAP (Table 13). The LS Mean (95% CI) CFB of weekly SBM was 1.84 (1.34, 2.34) in the placebo group, 2.22 (1.73, 2.70) in the low dose group, and 1.31 (0.82, 1.79) in the high dose group. The LS Mean difference (95% CI) in CFB of SBM per week during Part A, as compared to the placebo group, was 0.38 (-0.32, 1.07) in the low dose group and -0.54 (-1.23, 0.16) in the high dose group. The results of the MMRM analysis do not provide evidence that either prucalopride dose has an effect on the frequency of SBMs. Furthermore, the 95% CI of the treatment effect for the high dose group indicates that the observed data from the study would be extremely unlikely if the high dose meaningfully improved the frequency of SBMs. The MMRM model also provided estimates of the LS mean CFB in number of SBM at Week 12, and these estimates can be compared to the unadjusted means reported in Table 12. At Week 12, the LS Mean (95% CI) CFB of SBM per week was 1.90 (1.22, 2.59) in the placebo group, 2.45 (0.38, 1.71) in the low dose group, and 1.05 (0.38, 1.71) in the high dose group. The LS Mean difference (95% CI) in CFB of SBM per week, as compared to the placebo group, was 0.55 (-0.46, 1.57) in the low dose group and -0.86 (-1.81, 0.10) in the high dose group. These model-based results were consistent with the unadjusted results. The review team acknowledges that the reported estimates and confidence intervals based on the MMRM analysis may be biased because the study was terminated early for futility; however, any potential bias would likely be small and unlikely to substantively impact the conclusions. In general, the review team also notes that, despite some limitations, inferential analyses may still be informative in characterizing the magnitude of treatment effects that are consistent with the observed data in studies terminated early for futility.

Table 13: LS Mean Change from Baseline in Average Number of Weekly SBMs (Part A: Toilet-Trained Participants who were at Least 3 Years of Age) (Modified Intent-to-treat Analysis Set)

	Placebo N=52	Prucalopride Low Dose N=56	Prucalopride High Dose N=55
Week 1-Week 12, average			
CFB in SBM, LS Mean[a] (95% CI)	1.84 (1.34, 2.34)	2.22 (1.73, 2.70)	1.31 (0.82, 1.79)
LS Mean Difference[a] (95% CI)		0.38 (-0.32, 1.07)	-0.54 (-1.23, 0.16)
Week 12			
CFB in SBM, LS Mean[a] (95% CI)	1.90 (1.22, 2.59)	2.45 (0.38, 1.71)	1.05 (0.38, 1.71)
LS Mean Difference[a] (95% CI)		0.55 (-0.46, 1.57)	-0.86 (-1.81, 0.10)

Source: Reviewer generated using ADBOWEL.xpt
[a] LS means and corresponding differences were calculated using MMRM with treatment, age group, study week, and treatment-by-study week as fixed effects
Abbreviations: CFB: Change from baseline; CI: Confidence interval; LS: Least squares; MMRM: Mixed model with repeat measurements; N=number of subjects in population treatment group; SBM: spontaneous bowel movements

Data Quality and Integrity

The data were of sufficient quality to permit a substantive review.

Efficacy Results – Secondary and other relevant endpoints

The descriptive results for the secondary endpoint of CFB in weekly stool consistency at Week 12 are summarized in Table 14. In subjects < 8 years, the mean (SD) CFB in stool consistency at Week 12 was 0.6 (1.3) in the placebo group, 1.1 (0.7) in the low dose group, and 0.9 (0.6) in the high dose group. In subjects ≥ 8 years, the mean (SD) CFB in stool consistency at Week 12 was 1.3 (1.2) in the placebo group, 1.5 (1.7) in the low dose group, and 1.2 (1.3) in the high dose group. Overall, treatment did not have a clinically meaningful effect on stool consistency.

Table 14: Change from Baseline in Average Weekly Stool Consistency at Week 12 (Part A: Toilet-Trained Participants who were at Least 3 Years of Age) (Modified Intent-to-treat Analysis Set)

	Placebo		Prucalopride Low Dose		Prucalopride High Dose	
	Observed value	Change from baseline	Observed value	Change from baseline	Observed value	Change from baseline
Stool Consistency						
< 8 years						
n	10	10	9	9	8	8
n*	10	10	9	9	8	8
Mean[a] (SD)	3.7 (1.0)	0.6 (1.3)	3.7 (0.8)	1.1 (0.7)	4 (0.8)	0.9 (0.6)
Median[a]	4.0	1.0	4.0	1.0	4.0	1.0
≥ 8 years						
n	27	27	30	30	26	26
n*	27	25	30	30	26	26
Mean[a] (SD)	3.8 (1.4)	1.3 (1.2)	3.9 (1.3)	1.5 (1.7)	3.6 (1.3)	1.2 (1.3)
Median[a]	4.0	1.3	4.0	1.5	4.0	1.0

Source: IR Response Table 1 (4/14/25). Verified by reviewer using ADBOWEL-DATASET.xpt
[a] Mean (SD) and median were based on subjects with non-missing measurements
Abbreviations: IR=information request; n=number of subjects with at least 1 assessment during Week 12; n*=number of subjects with a non-missing measurement (i.e., ≥ 1 assessment during Week 12 and the screening period); SD=standard deviation

The descriptive results for the secondary endpoint of CFB in weekly average straining at Week 12 are summarized in Table 15. The mean (SD) CFB in straining at Week 12 was -0.8 (0.7) in the placebo group, -0.8 (0.7) in the low dose group, and -1.0 (0.7) in the high dose group. Overall, treatment did not have a clinically meaningful effect on straining.

Table 15: Change from Baseline in Average Weekly Straining at Week 12 (Part A: Toilet-Trained Participants who were at Least 3 Years of Age) (Modified Intent-to-treat Analysis Set)

	Placebo		Prucalopride Low Dose		Prucalopride High Dose	
	Observed value	Change from baseline	Observed value	Change from baseline	Observed value	Change from baseline
Weekly Straining						
n	37	37	39	39	34	34
n*	37	35	39	39	34	34
Mean[a] (SD)	0.6 (0.6)	-0.8 (0.7)	0.8 (0.6)	-0.8 (0.7)	0.5 (0.6)	-1.0 (0.7)
Median[a]	0.5	-1.0	1.0	-1.0	0.2	-1.0

Source: IR Response Table 2 (4/14/25). Verified by reviewer using ADBOWEL-DATASET.xpt
a Mean (SD) and median were based on subjects with non-missing measurements
Abbreviations: IR=Information Request; n=number of subjects with at least 1 assessment during Week 12; n*=number of subjects with a non-missing measurement (i.e., ≥ 1 assessment during Week 12 and the screening period); SD=standard deviation

The descriptive results for the secondary endpoint of response (i.e., ≥ 3 average weekly SBMs in at least 9 out of 12 weeks including at least 3 of the last 4 weeks and an increase of ≥ 1 SBM/week compared to baseline) are summarized in Table 16. The number of subjects with a response is low in each treatment group, with only 1 (1.9%) responder in the placebo group, 2 (3.6%) responders in the low dose group, and 0 responders in the high dose group. Although evaluation was limited by the relatively small number of subjects with 12 weeks of non-missing measurements, there appeared to be no substantive difference in the probability of response by treatment group.

Table 16: Proportion of Responders by Treatment Group (Part A: Toilet-Trained Participants who were at Least 3 Years of Age) (Modified Intent-to-treat Analysis Set)

	Placebo N=52	Prucalopride Low Dose N=56	Prucalopride High Dose N=55
Number of subjects with all 12 weeks of e-Diary data, n (%)	20 (38.5)	18 (32.1)	11 (20.0)
Number of subjects with a change of ≥1 average weekly SBMs compared to baseline at all 12 weeks, n (%)	2 (3.8)	2 (3.6)	0
Number of subjects with ≥3 average weekly SBMs in at least 9 out of 12 weeks including at least 3 of the last 4 weeks, n (%)	9 (17.3)	9 (16.1)	3 (5.5)
Proportion of responders[a], n (%)	1 (1.9)	2 (3.6)	0

Source: Clinical Study Report Table 11.u (page 108). Verified by reviewer using ADBOWEL.xpt
[a] A responder was defined as a participant having an increase of ≥1 SBM/week compared to baseline and ≥3 SBMs/week for at least 9 out of the 12 weeks of placebo-controlled part (Part A), including 3 of the last 4 weeks.
Abbreviations: e-Diary=electronic diary

Efficacy – Non-Toilet-Trained Subjects

Non-toilet-trained participants who were at least 6 months of age were included in an exploratory group given that the instruments used to evaluate the efficacy parameters were not considered fit-for-purpose in participants <3 years of age. In addition, the non-toilet-trained group was analyzed separately from the toilet-trained group, as it may be difficult to quantify BMs from diapers. Table 17 shows the results of efficacy endpoints at Week 12 in non-toilet-trained participants. Of note, there were 4 subjects in each arm. The limited sample size in this exploratory group precluded efficacy conclusions.

Table 17: Efficacy Endpoints at Week 12 in Non-Toilet-Trained Participants (Modified Intent-to-treat Analysis Set)

	Placebo N=4	Prucalopride Low Dose N=4	Prucalopride High Dose N=4
Number of subjects with Week 12 assessment	2	4	2
Average weekly SBM ≥ 3 and CFB in weekly SBM ≥ 1, n (%)	0	4 (100)	1 (50.0)
Average weekly SBM ≤ 1, n (%)	1 (50.0)	0	1 (50.0)

Source: Clinical Study Report End of Text Tables and Figures Table 15.3.2.6 (page 220) and Table 15.2.3.7 (page 223) Verified by reviewer using ADBOWEL.xpt
Abbreviations: N=number of subjects in population treatment group; SBM: spontaneous bowel movements

Dose/Dose Response

Refer to Section 6.3 Comprehensive Clinical Pharmacology Review.

Durability of Response

The efficacy data do not support a treatment effect at any timepoint.

Persistence of Effect

The efficacy data do not support a treatment effect at any timepoint.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Refer to Efficacy Results – Secondary and other relevant endpoints.

Additional Analyses Conducted on the Individual Trial

On August 28, 2023, the Sponsor submitted a request for a Type A meeting to discuss and gain agreement on the termination of Study TAK-555-3010 based on results from their interim analysis. In response, the Agency sent an Information Request on September 8, 2023, asking the Sponsor to perform simulations to evaluate the operating characteristics of their interim analysis. Specifically, the simulations were intended to evaluate the following four probabilities: 1) the probability of meeting the futility stopping criteria, 2) the probability of demonstrating superiority for at least 1 dose if the futility criteria are binding (i.e., the study is always stopped when the futility criteria are meet), 3) the probability of demonstrating superiority for at least 1 dose when there is no interim futility analysis, and 4) the probability of demonstrating superiority for at least 1 dose given the futility criteria are met but the study is continued. The results from these simulations are presented in Table 18. The results provide evidence supporting that study TAK-555-3010 was unlikely to meet the futility criteria if at least one dose showed a meaningful improvement and, if continued after meeting the futility criteria, the trial was unlikely to demonstrate superiority. Furthermore, the inclusion of the interim analysis for

futility did not substantively lower the overall probability of the trial's success. Therefore, these simulations support that the early termination of Study TAK-555-3010 based on the results of the interim analysis was reasonable.

Table 18: Simulations Results Evaluating the Operating Characteristics of the Interm Analysis

Scenario	Difference between prucalopride low dose and placebo in change from baseline in SBMs	Difference between prucalopride high dose and placebo in change from baseline in SBMs	Pooled standard deviation for change from baseline in SBMs	A	B	C	D	E
				Futility	Superiority when binding of futility and testing (either dose)	Superiority without IA (either dose)	Futility but superiority (joint)	Superiority given futility (conditional on Column A and study continuation)
1	0	0	2.5	0.7307	0.0223	0.0483	0.0261	0.0357
2	0	0.5	2.5	0.4887	0.1557	0.1812	0.0255	0.0522
3	0	1	2.5	0.1965	0.5757	0.6170	0.0413	0.2101
4	0	1.5	2.5	0.0421	0.9190	0.9430	0.0240	0.5686
5	0.5	0.5	2.5	0.3598	0.2508	0.2690	0.0182	0.0506
6	0.5	1	2.5	0.1624	0.6018	0.6313	0.0295	0.1814
7	0.5	1.5	2.5	0.0380	0.9192	0.9386	0.0195	0.5118
8	1	1	2.5	0.0889	0.7554	0.7793	0.0239	0.2692
9	1	1.5	2.5	0.0254	0.9404	0.9542	0.0138	0.5425
10	1.5	1.5	2.5	0.0099	0.9790	0.9856	0.0067	0.6707

Source: Table 2, Response to Information Request (9/13/23, SDN=471)

8.2. Review of Safety

8.2.1. Safety Review Approach

Review of safety focused on placebo-controlled data from the 12-week double-blind, placebo-controlled part (Part A) of Study TAK-555-3010. For Part A, the safety analysis set included all participants who received at least 1 dose of study drug in Part A. Safety data from the 36-week double-blind safety extension part (Part B) of Study TAK-555-3010 were also reviewed. For Part B, the safety analysis set included all participants who received at least 1 dose of study drug in Part B. The review team assessed adverse events of SI/SIB as AESIs and possible causal association to prucalopride use.

In addition, the review team considered the body of pre- and post-marketing safety data that have been collected and analyzed for prucalopride since its initial approval for adults with CIC in 2018 and a search was performed by the Division of Pharmacovigilance-I (DVP-I) for postmarketing reports of unlabeled psychiatric adverse events and serotonin syndrome.

8.2.2. Review of the Safety Database

Overall Exposure

In Study TAK-555-3010, 60 subjects were randomized to receive low dose prucalopride, 59

subjects were randomized to receive high dose prucalopride, and 56 subjects were randomized to receive placebo. Table 19 and Table 20 describe study drug exposure in Parts A and B, respectively, of Study TAK-555-3010.

Table 19: Study Drug Exposure (Part A) (Safety Analysis Set)

		Prucalopride		
	Placebo N=56	**Low dose N=60**	**High dose N=59**	**Overall N=119**
Length of exposure (Days)				
Mean (SD)	79.9 (20.51)	76.6 (22.90)	71.7 (26.36)	74.2 (24.69)
Median	85.0	84.0	84.0	84.0
Min, max	4.0, 122.0	1.0, 97.0	1.0, 102.0	1.0, 102.0

Source: Adapted from the Applicant's TAK-555-3010 Clinical Study Report Table 12.a

Table 20: Study Drug Exposure (Part B) (Safety Analysis Set)

	Prucalopride		
	Low dose N=72	**High dose N=62**	**Overall N=134**
Length of exposure (Days)			
Mean (SD)	193.9 (86.68)	191.8 (88.38)	192.9 (87.15)
Median	249.0	244.0	248.0
Min, max	1.0, 284.0	12.0, 287.0	1.0, 287.0

Source: Adapted from the Applicant's TAK-555-3010 Clinical Study Report Table 12.b

Adequacy of the Safety Database:

The Applicant's safety database was sufficient to characterize the safety profile in pediatric patients aged 6 months to 17 years with FC. In Part A, the Applicant's safety database contained placebo-controlled safety data from a total of 175 subjects. In Part B, the Applicant's safety database contained safety data from a total of 134 subjects, which was fewer subjects than originally planned (approximately 240 toilet-trained subjects [80 subjects per treatment arm] were planned to be included). The Applicant enrolled subjects across the entire age range of 6 months to 17 years prior to the study being terminated early, including 6 of the 12 non-toilet-trained subjects who were 6 months to <3 years. Pediatric safety data from the study were also reviewed in the context of the known safety profile of prucalopride in adults with CIC and found to be similar.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The review team did not identify any data integrity or submission quality issues.

Categorization of Adverse Events

Adverse Events (AEs) were coded with the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0. The review team compared verbatim terms with the Applicant's coded/preferred term to help ensure consistency in coding and the team made revisions as needed. Overall, the results of the team's analyses were similar to that of the Applicant; however, the team had to recode several terms prior to the analyses of the safety data. Refer to the Appendix, Supplementary Tables, Table 34 for information on the recoded terms for Study TAK-555-3010.

Routine Clinical Tests

The safety assessments included laboratory tests (hematology, serum chemistry, urinalysis, pregnancy), 12-lead electrocardiograms (ECG), vital sign measurements, and physical examinations. The routine clinical testing and safety monitoring appear to be adequate to ensure the safety of the subjects enrolled in the studies.

8.2.4. Safety Results

Overview of Subjects with Treatment-Emergent Adverse Events (TEAEs)

Table 21 and Table 22 summarize the numbers of subjects who experienced any TEAEs, serious TEAEs, TEAEs leading to dose discontinuation, and TEAEs leading to death in Part A and Part B of Study TAK-555-3010, respectively. In Part A, the rates of any TEAEs and TEAEs leading to dose discontinuation were higher in both the prucalopride low dose and high dose groups, as compared to the placebo group. In both Parts A and B, there were no dose-dependent increased rates of TEAEs.

Table 21: Treatment-Emergent Adverse Events Summary (Part A) (Safety Analysis Set)

		Prucalopride		
	Placebo N=56 n (%)	**Low Dose N=60 n (%)**	**High Dose N=59 n (%)**	**Overall N=119 n (%)**
Subjects with any TEAE	15 (26.8)	24 (40.0)	18 (30.5)	42 (35.3)
Subjects with serious TEAE	1 (1.8)	0	0	0
Subjects with TEAEs leading to dose discontinuation	2 (3.6)	5 (8.3)	3 (5.1)	8 (6.7)
Subjects with TEAEs leading to death	0	0	0	0

Source: Reviewer's table using adae dataset from Study TAK-555-3010

Table 22: Treatment-Emergent Adverse Events Summary (Part B) (Safety Analysis Set)

	Prucalopride		
	Low Dose N=72 n (%)	High Dose N=62 n (%)	Overall N=134 n (%)
Subjects with any TEAE	22 (30.6)	17 (27.4)	39 (29.1)
Subjects with serious TEAE	1 (1.4)	1 (1.6)	2 (1.5)
Subjects with TEAEs leading to dose discontinuation	1 (1.4)	1 (1.6)	2 (1.5)
Subjects with TEAEs leading to death	0	0	0

Source: Reviewer's table using adae dataset from Study TAK-555-3010

Deaths

No deaths were reported during the study.

Serious Adverse Events

Subject (b) (6) (placebo Part A - prucalopride low dose Part B) experienced an SAE of depression during Part A and SAEs of intentional self-injury and suicidal ideation during Part B, and these 3 SAEs were AEs of special interest (AESIs). Subject (b) (6) (placebo Part A - prucalopride high dose Part B) experienced an SAE of abdominal pain during Part B. The narratives and reviewer's assessments are discussed below.

- Subject (b) (6) is a 16-year-old female with medical history including constipation, anxiety disorder, autistic disorder, chromosome 16p13.3 deletion syndrome, chromosome 22q11.2 deletion syndrome, depression, dysphagia, gastroesophageal reflux disease, generalized muscle weakness, oppositional defiant disorder, and tic disorder. The subject had a history of engaging in self-injurious behavior for 2 years prior to enrolling in the study and was being monitored by a mental health provider. Concomitant medications during the study included Colace, Elinest, ibuprofen, Lexapro, melatonin, mupirocin, pantoprazole, Varibar nectar, Wellbutrin, and Zyrtec (cetirizine hydrochloride).

  The subject received placebo in Part A and low dose prucalopride in Part B. In Part A, the subject reported a serious TEAE of depression (moderate severity). In Part B, approximately 2 months after the TEAE of depression was reported, the subject reported a serious TEAE of intentional self-injury described as cutting and skin picking. On Day 119, the subject received the last dose of study drug, which was discontinued due to the study being terminated by the Applicant. On Day 121 (2 days after the last dose of the study drug), a serious TEAE of suicidal ideation was reported. The subject

reported that her depression had worsened over the last 3 months.

The subject was admitted to the hospital due to the serious TEAEs of depression, intentional self-injury, and suicidal ideation. On Day 143, the serious TEAEs were reported as resolved, and the subject was discharged from the hospital on the same day. Wellbutrin as treatment for depression was discontinued, and the subject was started on sertraline 100 mg/day.

There are known psychiatric risks with the 5-HT_4 receptor agonist class and SI/SIB were AESIs for this study. The approved prucalopride labeling includes a WARNINGS AND PRECAUTIONS subsection for suicidal ideation and behavior stating the following, in part:

> In clinical trials, suicides, suicide attempts, and suicidal ideation have been reported. Postmarketing cases of suicidal ideation and behavior as well as self-injurious ideation and new onset or worsening of depression have been reported within the first few weeks of starting MOTEGRITY.

Therefore, the serious TEAEs of depression, intentional self-injury, and suicidal ideation are labeled AEs; however, given this subject's history of depression and anxiety and concomitant use of serotonergic drugs (i.e., escitalopram, sertraline) with the administration of prucalopride, there is concern for additive serotonergic effects and exacerbation of underlying psychiatric history. There is mechanistic plausibility and temporal association for possible prucalopride-induced worsening of depression, anxiety, and self-injurious behavior that escalated to suicidal ideation and hospitalization 2 days after the last dose of the study drug. As the contribution of prucalopride was difficult to dissociate from the subject's concomitant medications and underlying psychiatric history, a description of this case was not included in labeling. The review team recommends continued pharmacovigilance, especially in the pediatric population for psychiatric adverse events, in particular SI/SIB.

- Subject (b) (6) is a 16-year-old female with medical history including discoid lupus erythematosus, gastroesophageal reflux disease, and polyarticular rheumatoid factor-positive juvenile idiopathic arthritis. Concomitant medications during the study included azithromycin, folic acid, hydroxychloroquine, meloxicam, methotrexate, Midol (caffeine; mepyramine maleate; paracetamol), omeprazole, and oseltamivir phosphate.

  The subject received placebo in Part A and high dose prucalopride in Part B. During Part B, on Day 88, a TEAE of abdominal pain was reported. The subject also experienced nonserious TEAEs of oropharyngeal pain and nausea. A test for group A Streptococcus was negative, and the TEAE of oropharyngeal pain resolved on the same day. The following day (Day 89), the subject was sent to the emergency room

due to lower abdominal pain. An x-ray showed small impaction of stool. The subject received bisacodyl 5 mg but never had a bowel movement. Nonserious TEAEs of constipation and vomiting were also reported; the TEAE of vomiting resolved on the same day. On Day 90, treatment with the study drug was paused. The participant confirmed that the abdominal pain got slightly better.

On Day 92, the subject was sent again to the emergency room, and an x-ray showed moderate stool. A SMOG (saline, mineral oil, glycerin) enema was given. On the same day, the subject was admitted to the hospital. The subject had not had a bowel movement for 5 days. The subject was given intravenous fluids, acetaminophen, and a saline (sodium chloride) enema. Two days later (Day 94), the subject was discharged from the hospital. On Day 97, the serious TEAE of abdominal pain and the TEAE of constipation resolved.

The abdominal pain is likely due to the subject's history of constipation and reported stool impaction. However, abdominal pain is a common adverse reaction (≥2%) with prucalopride use in both the adult trials supporting the CIC indication and is also a common TEAE in Study TAK-555-3010 (see Table 23 and Table 24 below). The subject's abdominal pain is possibly related to prucalopride.

This subject also reported two nonserious TEAEs of depressive symptoms. On Day 106, a nonserious TEAE of moderate depressive symptom was reported. Treatment with the study drug was interrupted due to the TEAE on Day 107 and resumed the following day. Two days later, the TEAE of depressive symptom resolved. On Day 200, a second nonserious TEAE of moderate depressive symptom was reported. Two days later, treatment with the study drug was discontinued due to the second TEAE of depressive symptom. The second TEAE of depressive symptom remained ongoing at the time of reporting.

The absence of prior history of depression, occurrence of 2 depressive events while on prucalopride treatment, positive dechallenge after temporarily interrupting the study drug with the first depression event are consistent with a probable causality of prucalopride. The existing labeling with a WARNINGS AND PRECAUTIONS for SI/SIB including new-onset or worsening of depression addresses this risk and no additional labeling is needed at this time. The review team recommends continued pharmacovigilance, especially in the pediatric population for psychiatric adverse events.

Dropouts and/or Discontinuations Due to Adverse Effects

In Part A, the most commonly reported TEAEs leading to discontinuation of study drug were vomiting (1/56 (1.8%) subject in the placebo group, 3/60 (5%) subjects in the prucalopride low dose group, and 0 subjects in the prucalopride high dose group) and decreased appetite (0 subjects in the placebo group, 1/60 (1.7%) subjects in the prucalopride low dose group, and 1/59 (1.7%) subjects in the prucalopride high dose group). Other TEAEs leading to

discontinuation of study drug were reported for at most 1 subject in the prucalopride or placebo groups.

In Part B, TEAEs leading to discontinuation of study drug were abdominal pain (1/72 (1.4%) subjects in the prucalopride low dose group and 0 subjects in the prucalopride high dose group) and depressive symptom (0 subjects in the prucalopride low dose group and 1/62 (1.6%) subjects in the prucalopride high dose group).

Of note, vomiting, decreased appetite, abdominal pain, and depression are labeled adverse reactions for prucalopride in adults. As shown in Table 21, in Part A, 2/56 (3.6%) subjects in the placebo group, 5/60 (8.3%) subjects in the prucalopride low dose group, and 3/59 (5.1%) subjects in the prucalopride high dose group, reported a TEAE leading to the discontinuation of study drug.

Slightly more subjects in the prucalopride groups discontinued study drug due to GI and psychiatric AEs, consistent with the known safety profile of prucalopride, compared to subjects in the placebo group.

Significant Adverse Events

Most TEAEs were mild or moderate in intensity. Severe TEAEs were reported as follows:

- In Part A, 1/59 (1.7%) subject in the prucalopride high dose group had a severe TEAE of hand fracture, likely unrelated to study drug treatment. None of the subjects in the prucalopride low dose or placebo groups had severe TEAEs.
- In Part B, 1/72 (1.4%) subject in the prucalopride low dose group had a severe TEAE of abdominal pain. Subject (b) (6) is a 15-year-old female with medical history of constipation and acne. Concomitant medications during the study included Accutane and docusate as rescue medication. Treatment with the study drug was discontinued due to the TEAE of abdominal pain, which later resolved. Abdominal pain is possibly related to the subject's prucalopride use given the temporal association and that abdominal pain is a labeled common adverse reaction (≥2%) with prucalopride use. The subject's history of constipation requiring rescue medication is likely contributing to the abdominal pain.
- In Part B, 2/62 (3.2%) subjects in the prucalopride high dose group had severe TEAEs of abdominal pain and fecaloma. Subject (b) (6) reported severe abdominal pain that was also serious, and this subject is discussed above under serious adverse events. Subject (b) (6) is a 12-year-old male who reported a severe fecaloma, likely caused by the subject's constipation.

Treatment Emergent Adverse Events and Adverse Reactions

The most common TEAEs, occurring in ≥2% of prucalopride-treated subjects, are provided in Table 23 (Part A) and Table 24 (Part B). The review team selected a threshold of ≥2% to capture AEs that occurred in more than a single subject. The most common TEAEs were similar in Parts

A and B, as well as in the pediatric and adult populations. Headache, vomiting, abdominal pain,[2] diarrhea, and nausea (nausea was reported with a similar incidence in prucalopride-treated and placebo subjects) were common adverse reactions reported by both pediatric subjects in Study TAK-555-3010 and adult subjects in the double-blind, placebo-controlled trials of CIC. The AEs not already labeled for the adult population are common events in pediatric patients, and based on the mechanism of action of prucalopride, are unlikely related to the study drug (e.g., upper respiratory tract infection, pyrexia, pain in extremity, seasonal allergy, influenza, oropharyngeal pain).

Table 23: TEAE Summary (TEAEs Occurring in ≥2% Prucalopride-treated Subjects and Greater than Placebo) (Part A) (Safety Analysis Set)

		Prucalopride		
Adverse Event	Placebo N=56 n (%)	Low Dose N=60 n (%)	High Dose N=59 n (%)	Total N=119 n (%)
Headache	3 (5.4)	8 (13.3)	5 (8.5)	13 (10.9)
Vomiting	2 (3.6)	8 (13.3)	4 (6.8)	12 (10.1)
Upper respiratory tract infection[1]	2 (3.6)	5 (8.3)	6 (10.2)	11 (9.2)
Abdominal pain[2]	2 (3.6)	5 (8.3)	3 (5.1)	8 (6.7)
Pyrexia	1 (1.8)	3 (5.0)	0	3 (2.5)
Pain in extremity	0	0	2 (3.4)	2 (1.7)
Seasonal allergy	0	2 (3.3)	0	2 (1.7)

Source: Reviewer's table using adae dataset from Study TAK-555-3010
[1] Upper respiratory tract infection includes nasopharyngitis, viral upper respiratory tract infection, pharyngitis, pharyngitis streptococcal, sinusitis, nasal congestion, and rhinorrhoea
[2] Abdominal pain includes abdominal pain lower and abdominal pain upper

Table 24: TEAE Summary (TEAEs Occurring in ≥2% Prucalopride-treated Subjects) (Part B) (Safety Analysis Set)

	Prucalopride		
Adverse Event	Low Dose N=72 n (%)	High Dose N=62 n (%)	Overall N=134 n (%)
Upper respiratory tract infection[1]	11 (15.3)	4 (6.5)	15 (11.2)
Headache	3 (4.2)	5 (8.1)	8 (6.0)
Abdominal pain[2]	3 (4.2)	4 (6.5)	7 (5.2)
Diarrhea	2 (2.8)	2 (3.2)	4 (3.0)
Influenza	0	2 (3.2)	2 (1.5)
Nausea	0	2 (3.2)	2 (1.5)
Oropharyngeal pain	0	2 (3.2)	2 (1.5)
Vomiting	0	2 (3.2)	2 (1.5)
Pyrexia	2 (2.8)	0	2 (1.5)

Source: Reviewer's table using adae dataset from Study TAK-555-3010
[1] Upper respiratory tract infection includes nasopharyngitis, viral upper respiratory tract infection, pharyngitis, pharyngitis streptococcal, sinusitis, nasal congestion, and rhinorrhoea
[2] Abdominal pain includes abdominal pain lower and abdominal pain upper

Laboratory Findings

Overall, there were no clinically significant mean changes from baseline in serum chemistry, hematology, or urinalysis parameters.

Vital Signs

Mean change from baseline in vital signs, including systolic and diastolic blood pressure, pulse rate, and body weight, were reviewed. Overall, no clinically significant vital sign abnormalities were observed.

Electrocardiograms (ECGs)

Overall, no clinically significant mean changes from baseline in clinical laboratory evaluations were reported during the study.

8.2.5. Safety Analyses by Demographic Subgroups

Table 25 below describes the proportion of subjects who experienced at least one TEAE, by demographic subgroups of sex, age category, and race. Overall, no trends were identified by the subgroup analyses; however, sample sizes for subgroups were too small to facilitate meaningful comparisons.

Table 25: Subjects with Any TEAE by Demographic Subgroup (Part A) (Safety Analysis Set)

Parameter	Placebo N=56 n (%)	Prucalopride Low Dose N=60 n (%)	Risk Difference (Prucalopride - Placebo)	Prucalopride High Dose N=59 n (%)	Risk Difference (Prucalopride - Placebo)
Sex					
Male	7/21 (33.3)	8/32 (25.0)	-8.3	8/31 (25.8)	-7.5
Female	8/35 (22.9)	16/28 (57.1)	34.2	10/28 (35.7)	12.8
Age category					
6 months to <3 years	0/1 (0)	2/3 (66.7)	66.7	2/2 (100.0)	100.0
≥3 years to <12 years	10/35 (28.6)	18/35 (51.4)	22.8	14/36 (38.9)	10.3
≥12 years	5/20 (25.0)	4/22 (18.2)	-6.8	2/21 (9.5)	-15.5
Race					
White	11/31 (35.5)	13/34 (38.2)	2.7	11/35 (31.4)	-4.1
Black or African American	3/23 (13.0)	9/22 (40.9)	27.9	7/23 (30.4)	17.4
American Indian or Alaska Native	0/0 (0)	0/1 (0)	0	0/1 (0)	0
Multiple	0/0 (0)	1/2 (50.0)	50.0	0/0 (0)	0
Not Reported	1/2 (50.0)	1/1 (100.0)	50.0	0/0 (0)	-50.0

Source: Reviewer's table using adae dataset from Study TAK-555-3010

8.2.6. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

During the review of this pediatric efficacy supplement, DG consulted DPV-I to conduct 1) an evaluation of the FAERS database and medical literature from June 4, 2020, through November 4, 2024, for postmarketing reports of unlabeled psychiatric adverse events with prucalopride, and 2) an evaluation of postmarketing reports of serotonin syndrome with prucalopride received to the FAERS database through November 4, 2024.

Previous DPV-I Reviews

The following is a summary of previous DPV-I reviews which informed the current review:

- DG consulted DPV-I on March 30, 2020 to evaluate if there have been additional reports of SIB in the postmarketing setting since the time of product approval based on the FDA Adverse Event Reporting System (FAERS) and medical literature, and to provide input on the strength of the evidence to support Applicant's proposal to revise the labeling in Section 5.1 *Suicidal Ideation and Behavior* to state that SIB events have occurred in the postmarketing setting. The DPV team identified 8 cases of SIB/self-injurious behavior and 14 cases of new-onset or worsening of underlying psychiatric disorders (e.g., anxiety, depression, mood instability, nightmares, panic attacks, visual hallucinations). Refer to the review by Jamie Ridley Klucken, PharmD, MBA, BCPS, BCACP, in DARRTS, dated June 29, 2020, for discussion on these psychiatric events and possible contribution of prucalopride. Based on review of these cases, the WARNINGS AND PRECAUTIONS section of prucalopride labeling was updated to reflect the potential risk of SIB and self-injurious behavior in patients with and without a past medical history of psychiatric disease and the *Postmarketing Experience* section was updated to list the following events: suicide, suicide attempts, suicidal ideation, self-injurious ideation, depression, anxiety, insomnia, nightmares, and visual hallucinations. Refer to the clinical review by Irena Lavine, MD, in DARRTS, dated November 6, 2020.

- On August 5, 2021, DPV-I completed a postmarket drug safety surveillance summary of prucalopride, (b) (4)

(b) (4) The team agreed that the label adequately described the risk of SIB in adults. The three cases of suicidal ideation in pre-adolescents and adolescents during off-label use of prucalopride were addressed by (1) a protocol amendment to add SIB to data collection, as an AESI; (2) updated investigator brochure and informed consent to include SIB; and (3) recommendations from the Division of Psychiatry regarding subject protection and how to improve the inclusion/exclusion criteria for patient enrollment, and the quality of data collection in the PMR study protocol. Refer to the postmarket drug safety surveillance summary by Paolo Fanti, MD, in DARRTS, dated August 5, 2021.

Current DPV-I Review

Postmarketing reports of unlabeled psychiatric adverse events and serotonin syndrome identified in adults by DPV-I in the FAERS database between June 4, 2020, and November 4, 2024 are summarized below. No cases were identified in pediatric patients.

Refer to the complete consult by Laura Kangas, PharmD, BCPS in DARRTS, dated May 20, 2025.

Unlabeled Psychiatric Adverse Events

DPV-1 identified two cases of unlabeled psychiatric events that are summarized below.

- FAERS Case #22323842: A 27-year-old female with no history of anxiety reported progressively worsening anxiety, derealization, restlessness, and unprovoked angry outbursts “a few months” after initiating prucalopride 2 mg daily for CIC. Concomitant medications and supplements included Estarylla (norgestimate and ethinyl estradiol tablet), magnesium, apple cider vinegar gummies, and vitamin C gummies. The patient’s symptoms increased in frequency and, after approximately 9 months of prucalopride use, culminated in a severe panic attack that lasted over 1 hour and required sedative administration by her husband, a neurologist, who diagnosed hyperreflexia and sweaty palms and feet. Prucalopride was discontinued with symptom resolution.

  This case describes the unlabeled events of angry outbursts, derealization, and panic attack with possible causal association to prucalopride use. DPV assessed the case as limited by extended time to symptom onset and lack of diagnostic information and assessment for alternative etiologies. Anxiety is currently listed in the *Postmarketing Experience* subsection of labeling. The review team does not recommend adding panic attack to the labeling based on this one case with limited information.

- FAERS case# 22105396: A 52-year-old male with a history of depression, generalized anxiety disorder, and benign prostatic hypertrophy was initiated on prucalopride 2 mg daily for constipation associated with irritable bowel syndrome (IBS). Concomitant medications and supplements included medical cannabis, dicyclomine, tamsulosin, and escitalopram; patient previously tolerated 1 year of escitalopram therapy several years prior. One month after prucalopride initiation, he started experiencing racing thoughts,

insomnia, increased irritability, and exhibited erratic and confrontational behavior that endangered his safety. Two months after prucalopride initiation, the patient was hospitalized for symptoms of acute mania with psychotic features. Laboratory test results were unremarkable, including complete blood count, basic metabolic panel, and liver function tests and vitamin B12, ethanol, thyroid stimulating hormone levels. On hospital day 1, escitalopram was discontinued, and olanzapine was initiated; on hospital day 7, clonazepam was initiated for insomnia; on hospital day 8, lithium was initiated for persistent euphoric mania and insomnia; the patient continued to have symptoms of acute mania. On hospital day 13, prucalopride was discontinued; by hospital day 15, the patient's sleep had improved, and his thought process was more goal-directed. On hospital day 20, he was discharged home.

This published case describes acute mania with psychotic features with a possible causal relationship to prucalopride based on temporality and positive dechallenge with medication treatment. However, DPV noted that there are multiple confounding factors, including concomitant use of escitalopram[12] and cannabis,[13] both of which are risk factors for mania. In addition, the resolution of the patient's symptoms occurred within 2 days of prucalopride discontinuation, but also coincided with the time that olanzapine and lithium reached therapeutic levels and escitalopram discontinuation. Therefore, given the multiple confounding factors as well as only one known case of mania, the review team does not recommend adding mania to the labeling for prucalopride.

Serotonin Syndrome

DPV-I identified two postmarketing cases of serotonin syndrome with a possible causal association to prucalopride use. The patients were both taking concomitant serotonergic drugs that can cause serotonin syndrome alone or in combination with other serotonergic drugs (i.e., IV tramadol, venlafaxine) and there were limited details provided for the diagnosis of serotonin syndrome. In addition, serotonin syndrome is primarily associated with substances that stimulate postsynaptic 5-hydroxytryptamine $(5\text{-HT})_{2A}$ receptors;[14] prucalopride is a 5-HT_4 receptor agonist and was devoid of effects mediated via 5-HT_{2A} receptors in vitro at

[12] Risk of activation of mania/hypomania is described in the WARNINGS AND PRECAUTIONS section (5.5) of the labeling for Lexapro.
Lexapro [Prescribing Information]. AbbVie Inc, North Chicago, IL. Label revised October 2023. Accessed March 21, 2025, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/021323s058lbl.pdf.
[13] Henquet C, Krabbendam L, de Graaf R, ten Have M, and van Os J. Cannabis use and expression of mania in the general population. J Affect Disord 2006; 95:103-10.
[14] Isbister GK, Buckley NA. The pathophysiology of serotonin toxicity in animals and humans: implications for diagnosis and treatment. Clin Neuropharmacol 2005 Sep-Oct;28(5):205-14.

concentrations exceeding 5-HT_4 receptor affinity by at least 150-fold.[15] Therefore, the review team does not recommend labeling prucalopride for serotonin syndrome.

8.3. Statistical Issues

No additional statistical issues were identified.

8.4. Conclusions and Recommendations

Study TAK-555-3010 was conducted under PREA as a PMR to assess the safety and efficacy of prucalopride in pediatric patients 6 months to < 18 years with FC. The interim analysis of the primary efficacy endpoint showed that the number of SBMs per week over 12 weeks was similar between the prucalopride and placebo groups, indicating that the study was unlikely to demonstrate effectiveness. Therefore, the study was terminated early for futility. Based on the results of the primary and secondary endpoints, there is no evidence of effectiveness for either prucalopride dose in pediatric patients 6 months to 17 years of age and the study appears to have been unlikely to show a significant treatment benefit had the study fully enrolled.

No deaths occurred in Study TAK-555-3010, and SAEs were rare overall. No new safety signals were identified from the submitted pediatric study data. The safety profile of prucalopride in the studied pediatric population was similar to the known safety profile in the adult population with CIC. No postmarketing reports of unlabeled psychiatric adverse events or serotonin syndrome were identified.

The Applicant did not request a pediatric indication for FC based on the results for Study TAK-555-3010. Instead, the study will be summarized in the *Pediatric Use* subsection of the label to state that safety and effectiveness of prucalopride in pediatric patients with FC have not been established and the adverse reactions reported in pediatric patients in the study were similar to those reported in adults in trials of CIC. The Division considers that the Applicant did due diligence to design and conduct the study to demonstrate safety and effectiveness of prucalopride in pediatric subjects. The Applicant enrolled subjects across the entire age range of 6 months to < 18 years prior to the study being terminated early, including 6 of the 12 non-toilet-trained subjects who were 6 months to <3 years. Therefore, the Division considers the study adequate to fulfill PMRs 3529-1 and 3529-6.

[15] Motegrity (prucalopride) [Prescribing Information]. Takeda Pharmaceuticals America, Inc. Lexington, MA: Label revised November 2020. Accessed February 3, 2025, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210166s002lbl.pdf

9 Advisory Committee Meeting and Other External Consultations

Not applicable.

10 Pediatrics

This application NDA 210166/S-004 was presented to the Pediatric Review Committee (PeRC) on June 17, 2025. PeRC agreed with the team's proposed updates to Section 8.4 *Pediatric Use* subsection of the PI to state that safety and effectiveness have not been demonstrated, as well as the brief description of the findings from Study TAK-555-3010.

PeRC also agreed with the team's recommendation, that the study was adequate to fulfill PMRs 3529-1 and 3529-6.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant proposed the following for section 8.4 *Pediatric Use* of the Motegrity label.

> The safety and effectiveness of MOTEGRITY have not been established in pediatric patients. (b) (4) evaluated in a 12-week randomized, double-blind, (b) (4) placebo-controlled study (b) (4) followed by a 36-week double-blind extension study (b) (4)

The review team proposed minor edits to the description of the study for brevity, defined the primary endpoint, and discussed the results of the interim analysis as shown.

> The safety and effectiveness of MOTEGRITY have not been established in pediatric patients. MOTEGRITY was evaluated in a 12-week randomized, double-blind, placebo-controlled study, followed by a 36-week double-blind extension study in patients 6 months to 17 years with functional constipation. The interim analysis of the primary endpoint showed that the number of spontaneous bowel movements per week over 12 weeks was similar between the MOTEGRITY and placebo groups, indicating that the study was unlikely to demonstrate effectiveness. Therefore, the study was terminated

early for futility. Adverse reactions reported in pediatric patients in this study were similar to those reported in adults.

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable

13 Postmarketing Requirements and Commitment

Study TAK-555-3010 was conducted to fulfill PMRs 3529-1 and 3529-6.

PMR 3529-1 Evaluate the pharmacokinetics, efficacy, and safety of Motegrity (prucalopride) in pediatric patients with chronic idiopathic constipation (CIC) who are 6 months to less than 18 years of age by performing a randomized, double-blind, placebo-controlled, parallel group, 12-week treatment study.

PMR 3529-6 Assess the long-term safety of Motegrity (prucalopride) in pediatric patients with chronic idiopathic constipation (CIC) who are 6 months to less than 18 years of age and have completed a confirmatory efficacy and safety study with Motegrity (prucalopride) by performing a safety and tolerability study comparing two doses in a blinded design.

The review team recommends fulfillment of PMRs 3529-1 and 3529-6 based on the results of Study TAK-555-3010. No postmarketing requirements or commitments are recommended as a result of this review.

The pediatric studies requirement for ages birth to less than 6 months of age was partially waived because necessary studies are impossible or highly impracticable. This is because of the limited number of patients less than 6 months of age with FC who require pharmacologic therapy and the complexities of studying this patient population.

14 Appendices

14.1. References

Not appliable

14.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study TAK-555-3010

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 122		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.3. Nonclinical Pharmacology/Toxicology

Not applicable

14.4. OCP Appendices (Technical documents supporting OCP recommendations)

14.4.1. Bioanalytical Method Validation and In-Study Analysis Report

Prucalopride concentrations in human plasma samples from Study TAK-555-3010 were analyzed via a validated LC-MS/MS detection method (bioanalytical method validation report P1754). The analytical range of the assay was 0.05 to 50.0 ng/mL. The LC-MS/MS method was newly developed with a greater sensitivity compared that that submitted with the original NDA (e.g., A6425M-SPD555, A6425-SPD555). The method validation summary results are summarized in Table 26. The accuracy (% bias) and precision (% coefficient of variation [%CV]) of all validation parameters met the acceptance criteria.

Table 26: Summary of Validation Parameters for Bioanalytical Method P1754

Validation Parameters	Results
Analyte	Prucalopride
Assay Range (standard curve concentrations)	0.05 – 50.0 ng/mL
Standard curve concentrations	0.0500, 0.100, 0.200, 0.800, 3.00, 12.0, 40.0, and 50.0 ng/mL
Assay Matrix	Human Plasma
QC concentrations	0.0500, 0.150, 7.50, 20.0, and 37.5 ng/mL
QC Intra-assay Accuracy (%Bias)	-2.86 – 7.62%
QC Intra-assay Accuracy (% CV)	1.17 – 5.88%
QC Inter-assay Accuracy (%Bias)	0.37 – 2.21%
QC Inter-assay Precision (%CV)	1.88 – 6.73%
Dilutional Linearity	20.0 ng/mL diluted 2.5-fold (bias: -0.174%, CV: 2.06%) 100 ng/mL diluted 10-fold (bias: 1.76%, CV: 1.71%)
Freeze-thaw Stability (cycles)	Five cycles frozen in a -20 °C freezer or -70 °C cryofreezer and thawed at room temperature
Thawed Matrix Stability (hours)	24.16 hours at room temperature
Frozen Matrix Storage Stability (days)	11 days in a -20 °C freezer and -70 °C cryofreezer
Stability in Frozen Matrix	611 days at -25°C freezer (bias: -1.58 to -7.6%; CV: 5.66 – 6.41%) and -80°C cryofreezer (bias: -0.393 to 2.13%; CV: 3.01 – 5.49%). Source: Method validation P1754 addendum 1 report
Whole Blood Stability	Two hours at room temperature and two hours in an ice bath prior to processing to plasma in a room temperature or refrigerated centrifuge

Validation Parameters	Results
Prucalopride Solution Stability (days)	100 µg/mL: 18 days in a -20°C freezer in methanol 5.00 µg/mL: 17 days in a -20°C freezer in methanol
Prucalopride Solution Stress Stability (hours)	100 µg/mL: 23.9 hours at room temperature in methanol 5.00 µg/mL: 23.9 hours at room temperature in methanol
Hemolysis (2% whole blood in plasma)	No effect from hemolysis on the quantitation of prucalopride.
Lipemia	No effect from lipemia on the quantitation of prucalopride.
Selectivity	No significant interfering peaks noted in blank human plasma samples.
Matrix Factor	Lot-to-lot response consistency was demonstrated for prucalopride.

Source: Bioanalytical method validation report and its addendum available at m5.3.1.4-seq 506

The in-study method performance for this study (TAK-555-3010) is briefly described in Table 27 below and is acceptable.

Table 27: Bioanalytical Method In-Study Performance Summary

Parameters	Results (Study TAK-555-3010)
Standard curve performance	Precision (%CV): 1.46% to 4.92% Accuracy (%Bias): -11.9% to 6.03%
QC performance QC levels: 0.150, 7.50, 20.0, and 37.5 ng/mL	Inter-Assay Precision (%CV): 1.37% to 2.75% Inter-Assay Accuracy (%Bias): -9.87% to 2.29%
Method reproducibility	Incurred sample re-analysis (ISR) was performed on 11.1% of the study samples. Total % ISR samples pass: 100%. Incurred sample repeats were considered acceptable if the original and re-assay values from two-thirds of the repeated samples had a relative percent difference of ≤ ±20%.

Source: Bioanalytical Report of sample analysis available at m5.3.5.1-Seq506, Appendices-16.1.10

14.4.2. Population Pharmacokinetic Analysis

The Applicant conducted population pharmacokinetic (PopPK) analysis using pooled data from the three pediatric studies to characterize the PK of prucalopride in pediatric subjects aged 1 to 17.96 years with functional constipation and to evaluate the impact of various covariates on the PK. The current final PopPK model is a two-compartment disposition model describing first-order elimination and first-order sequential absorption process (Table 28). This model is the same as the previous model for pediatric subjects. The post-hoc individual PK parameters

estimated based on the final PopPK model were used to generate PK exposures at steady state (Cmax,ss and AUCss) for each pediatric subject in the three pediatric studies including the PK Study TAK-555-3010 pooled for PopPK analysis. The exposures between pediatric subjects and adults were evaluated. No dose/exposure-response analysis was conducted as the study failed to demonstrate meaningful efficacy in the interim futility analysis at Week 12. Results from the PopPK analysis are summarized below:

- Body weight (BW) was identified as a significant predictor of prucalopride PK. Clearance and volume of distribution increased with increasing body weight with a range of 11 – 110 kg.

- The predicted median Cmax,ss and AUCss of Study TAK-555-3010 were generally higher in high-dose group (0.08 mg/kg QD if body weight [BW] <50 kg; 4 mg QD if BW ≥50 kg) compared to that of low-dose group (0.04 mg/kg QD if BW <50 kg; 2 mg QD if BW ≥50 kg). However, dose-normalized predicted Cmax,ss and AUCss were lower in high dose group compared to that in low dose group, which may be attributed to the higher mean body weight in the high dose group and sparse PK sampling.

- However, overall dose-normalized predicted Cmax,ss and AUCss across the three pediatric studies are comparable suggesting dose-proportional PK in pediatric subjects over the evaluated dose range.

- Predicted Cmax,ss and AUCss in low dose group of Study TAK-555-3010 were comparable with those of adults receiving the approved dosing regimen of 2 mg QD. In contrast, these are higher in high dose group compared to that of adult 2 mg QD. However, the overall predicted exposures in high dose group of pediatric subjects do not generally exceed those associated with 4 mg QD in healthy adult subjects.

- No labeling changes are proposed based on this PopPK analysis and submitted pediatric studies. A pediatric indication is not being sought by the Applicant as the drug failed to demonstrate efficacy during interim analysis at Week 12 and the study was stopped early for futility.

Table 28: Summary of PopPK Analyses

General Information	
Objectives of PopPK analysis	• To develop a population PK model to describe the PK of prucalopride and evaluate the effect of covariates on the PK. • To estimate exposures (AUC over a dosing interval at steady state [AUCss], maximal concentration at steady state [Cmax,ss]) using individual post-hoc PK parameters from Study TAK-555-3010 and compare the exposures of low and high dose groups with exposure estimates in adults following 2 mg once daily (QD) dose of prucalopride. • To simulate exposure estimates (AUCss, Cmax,ss) following TAK-555-3010 dosing regimens in pediatrics by using the Empirical Bayes estimates (EBEs)

	obtained from the three pediatric studies and compare them with exposure estimates in adults following 2 mg QD prucalopride.	
Study, population, Doses, and PK concentrations included in the PopPK dataset	The PopPK analysis dataset contained data from three pediatric studies described in Table 29. The source dataset contained a total of 833 PK concentrations from 219 subjects. The final PopPK analysis included at total of 774 PK concentrations from 195 subjects, as 59 concentration records were excluded from the source dataset due to the following reasons: • 37 due to BLQ (study 3010/303) • 21 due to missing time relative to sampling (study 303) • 1 due to unusually high concentration at 21 hour (study 303) Of the 774 prucalopride concentrations, 481 were from 38 subjects in Study PRU-USA-12, 243 were from 137 subjects in Study SPD555-303 and 50 were from 20 subjects in Study TAK-555-3010.	
Population Characteristics	See Table 30	
Final Model	**Summary**	**Acceptability [FDA's Comments]**
Software and version	• Nonlinear mixed effects modeling (NONMEM) (Version 7.5.0); PDx-Pop (Version 5.3.0) • R statistical software (version 4.1.2) was used for data presentation and construction of plots.	**Acceptable**
Model Structure	An existing PopPK model developed previously using data from Studies PRU-USA-12 and SPD555-303 was used to re-estimate PK parameters after including data from TAK-555-3010. The existing model is a two-compartment model with first-order sequential absorption and linear elimination. The model was parameterized in terms of CL/F, Vc/F, Q/F, Vp/F. The absorption of prucalopride following oral administration was described by a sequential first-order absorption process with one absorption rate (Ka1) before an estimated cut-off time and a second absorption rate (Ka2) after this cut-off time. Weight-based allometric scaling was applied on CL and V parameters and a maturation function was applied to CL. Inter-individual variability (IIV) was included on all structural parameters. Separate residual errors were estimated on Studies PRU-USA-12 (phase 1) and combined SPD555-303 and TAK-555-3010 (phase 3). Monte Carlo Importance Sampling Expectation Maximization (EM) was used in all models. A full variance-covariance matrix was implemented to allow full utilization of the efficient maximization process within the expectation maximization estimation methods. Note that Study PRU-USA-24 was initially planned to be included in the Applicant's analysis but was excluded due to the model being destabilized and failing to converge following addition of Study PRU-USA-24 data.	**Acceptable**

Base Model Parameters	The existing model served as the starting point. Body weight on CL/F, Vc/F, Vp/F, and Q/F and maturation of renal filtration rate using post menstrual age (PMA) on CL/F were included as covariates with the base model. See Table 31 for final parameter estimates.	**Acceptable**
Covariate model parameters	In addition to body weight and maturation of renal filtration rate at baseline as included in the base model, following covariates were evaluated: • Age, estimated glomerular filtration rate (eGFR), gender, formulation, and study effect.	**Acceptable**
Final Model Parameters	The final PK model was a two-compartment disposition model with sequential first-order absorption processes and first-order elimination. On average, CL/F, Vc/F, Q/F and Vp/F all scaled proportionally with weight, fixed to allometric scalars. Additionally, the model incorporated renal maturation function on CL for subjects below the age of 2 years. Since there were two pediatric subjects aged less than 2 years in the data, maturation function was retained in the model to depict the relationship between age and clearance rate. **See Table 31 for parameter estimates.** The structural PK parameter estimates (CL/F, Vc/F, Q/F and Vp/F) were estimated with good precision with %RSE ranging from 3 to 16% for all estimated parameters. The estimates of IIV were generally low to moderate, with coefficients of variation (CV) ranging from 17% to 38% for all parameters except for Ka1 and Ka2, which had high CVs of 156% and 121%, respectively. The high CVs for absorption parameters were anticipated due to the sparse sampling schemes in Studies SPD555-303 and TAK-555-3010. IIVs on Ka1 and Ka2 were not estimated in the final model. Ka1 and Ka2 parameters were fixed to the values obtained from a model using Study PRU-USA-12 (phase 1 with intensive PK sampling). The %RSE for all IIVs were <50% except for Q/F and Vp/F, which had high %RSE of 160% and 55.6%, respectively. Low precision in IIV for Q/F and Vp/F is possibly due to only 2-3 samples per each subject in Studies SPD555-303 and TAK-555-3010. The shrinkage (SD) of individual random effects was low for CL/F (19%) and for other parameters shrinkages were estimated at 51% for Vc/F, 59% for Q/F, 53% for Vp/F, 45% for Ka1, and 49% for Ka2.	**Acceptable**
GOF, VPC plots	The goodness-of-fit plots and VPC (visual predictive check) plots of the final population PK model are shown in Figure 3**, and** Figure 4**,** respectively.	**Acceptable**
Effect of Covariates	Body weight was the significant covariate influencing the PK of prucalopride. On average, CL/F, Vc/F, Q/F and Vp/F all increased with body weight following the scaling relationship $(WT/70)^{0.75}$ for CL/F and Q/F, and $(WT/70)^{1}$ for Vc/F and Vp/F.	**Acceptable**

Source: The Applicant's population pharmacokinetic analysis report available at m5.3.3.5-seq 0506
Ka: absorption rate constant; CL/F: Apparent clearance; Vc/F: Apparent volume of distribution for the central compartment; Vp/F: Apparent volume of distribution for the peripheral compartment (Vp/F); Q/F: Apparent inter-compartmental clearance

Table 29: Clinical Studies included in PopPK Analysis

Protocol No.	Population [N]	Design	Dosage/Regimen /Duration/Frequency	PK sampling
TAK-555-3010	Pediatric subjects (aged 6 months to 17 years) with functional constipation. N = 20 (PK subset)	Phase 3, Randomized, DB, PC study to evaluate efficacy and safety. PK was evaluated in a subset of patients	Low Dose: • BW <50 kg: 0.04 mg/kg QD • BW ≥50 kg: 2 mg QD High Dose: • BW <50 kg: 0.08 mg/kg QD • BW ≥50 kg: 4 mg Low and high dose are capped at 2 and 4 mg, respectively.	Day 0 (baseline): 1 – 3 h post-dose Day 28, 56, and 84: between 14 – 26 h post-dose, but before next dose.
SPD555-303	Pediatric subjects (aged 6 months to <18 years) with functional constipation. N = 137 (with PK)	Phase 3, Randomized, DB, PC study to evaluate efficacy, safety, tolerability, and PK	• BW <50 kg: 0.04 mg/kg QD; at Week 4, dose adjusted to 0.02/0.04/0.06 mg/kg depending on the response and/or safety/tolerability • BW ≥50 kg: 2 mg (tablet). No dose adjustment. • 8 weeks PC part, and 16 weeks AC part	Day 0 (baseline): 1 – 3 h post-dose Day 57, and 169: between 14 – 26 h post-dose
PRU-USA-12	Pediatric subjects (aged ≥4 and ≤ 12 years) with functional constipation N = 38	Phase 1, open-label single-dose PK study	• 0.03 mg/kg, oral solution	0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 48 and 72 h post-dose.

Source: Adapted from the applicant's PopPK report, Table 3-1
DB: double-blind, PC: placebo-controlled, AC: active-comparator, QD: once daily
Note that PK data from an additional study (PRU-USA-24, open-label extension of PRU-USA-12) were added and the PK parameters were re-estimated. However, the model was destabilized and did not converge. Therefore, data from study PRU-USA-24 were not retained in the present PopPK analysis

Table 30: Summary of Demographics and Baseline Characteristics for Pediatric Subjects Included in the Population Pharmacokinetic Analyses

		Study			
Covariate	**Statistic**	**PRU-USA-12**	**SPD555-303**	**TAK-555-3010**	**Overall**
	Number of Subjects (%)	38 (19)	137 (70)	20 (10)	195
	Number of concentration records (%)	481 (62)	243 (31)	50 (7)	774
Age (yr)	Mean (SD)	8.16 (2.53)	8.29 (4.38)	8.05 (4.12)	8.24 (4.04)
	Median (Min-Max)	8.50 (4.00-12.0)	7.86 (1.65-18.0)	9.00 (1.00-14.0)	8.00 (1.00-18.0)
Postmenstrual age (week)	Mean (SD)	464 (132)	471 (228)	459 (214)	468 (210)
	Median (Min-Max)	482 (248-664)	448 (126-974)	508 (92.0-768)	456 (92.0-974)
BL Weight (kg)	Mean (SD)	30.0 (11.3)	32.4 (20.2)	38.0 (21.5)	32.5 (19.0)
	Median (Min-Max)	27.8 (15.0-61.0)	24.0 (11.0-110)	41.0 (11.3-94.5)	26.5 (11.0-110)
BL eGFR ($mL/min/1.73m^2$)	Mean (SD)	167 (13.4)	156 (18.7)	156 (16.7)	158 (18.0)
	Median (Min-Max)	163 (148-216)	157 (93.6-210)	154 (132-186)	158 (93.6-216)
Gender N (%)	Female	13 (34.2)	79 (57.7)	10 (50)	102 (52.3)
	Male	25 (65.8)	58 (42.3)	10 (50)	93 (47.7)
Race N (%)	White/Caucasian/Hispanic	32 (84.2)	130 (94.9)	14 (70)	176 (90.3)
	Black or African-Amer	1 (2.6)	3 (2.2)	4 (20)	8 (4.1)
	Multiple/Other	2 (5.3)	1 (0.7)	1 (5)	4 (2.1)
	Not reported	3 (7.9)	3 (2.2)	1 (5)	7 (3.6)
Formulation N (%)	Oral Solution	38 (100)	111 (81)	15 (75)	164 (84.1)
	Tablet	-	26 (19)	5 (25)	31 (15.9)
[a]Dose group N (%)	Low dose	-	-	8 (40)	8 (4.1)
	High dose	-	-	12 (60)	12 (6.2)

Source: The Applicant's PopPK analysis report. The Reviewer's independent analysis using pruppkv2.xpt dataset found similar covariate distribution as tabulated.

[a] Low and high dose groups only in Study TAK-555-3010

Table 31: Pharmacokinetic and Covariate Parameters in Final Population PK Model

Model Parameter (Unit)	Population Estimate[a] (%RSE[a]) [95% CI[a]]	IIV Point Estimate (%CV[b]) {%RSE[c]} [Shrinkage[e]]
CL/F (L/hr)	21.7 (2.91) [20.5 – 22.9]	0.105 (32.5) {23.4} [18.6%]
V_c/F (L)	431 (3.61) [401 – 462]	0.028 (16.7) {38.7} [50.7%]
V_p/F (L)	248 (9.59) [206 – 300]	0.147 (38.3) {55.6} [53.1%]
Q/F (L/day)	18.4 (15.7) [13.5 – 25.1]	0.0517 (22.7) {160} [59.0%]
Ka1 (hr^{-1}))	0.792 Fixed	1.24 (156) {28.6}) [45.2%]
Ka2 (hr^{-1})	3.87 Fixed	0.898 (121) {43.1} [48.6]
CL/F~BW and Q/F~BW	0.75 Fixed	-
Vc/F~BW and Vp/F~BW	1 Fixed	-
MTIME (hr)	0.734 Fixed	-
F1 (%)	0.858 Fixed	-
Hill coefficient[d]	3.4 Fixed	-
TM_{50}[d] (week)	47.7 Fixed	-

Residual variability	Point Estimate	95% CI	%CV	%RSE
σ^2_{prop}, PRU-USA-12	0.14	0.127 – 0.152	14%	4.67
σ^2_{prop}, SPD555-303 and TAK-555-3010	0.358	0.294 – 0.422	36%	9.18

[a]Back-transformed from natural log scale (except for σ^2 and CL/F~BW, Vc/F~BW, Vp/F~BW, and Q/F~BW, MTIME, Hill coefficient and TM_{50}).
[b]CV for IIV calculated as CV_{TVP}= SQRT{EXP(ω^2_P)}*100 if $\omega^2_P \leq 0.15$, else CV_{TVP} = SQRT{EXP(ω^2_P)-1}*100, where ω^2_P is the variance of random effect on the parameter P.
[c]RSE for IIV and σ^2 calculated as |SE/Typical value|*100.
[d]Parameters were taken from Rhodin et al.[16] and were used in the model with maturation function.
[e]SD, p-value for the null hypothesis that the true mean is 0.

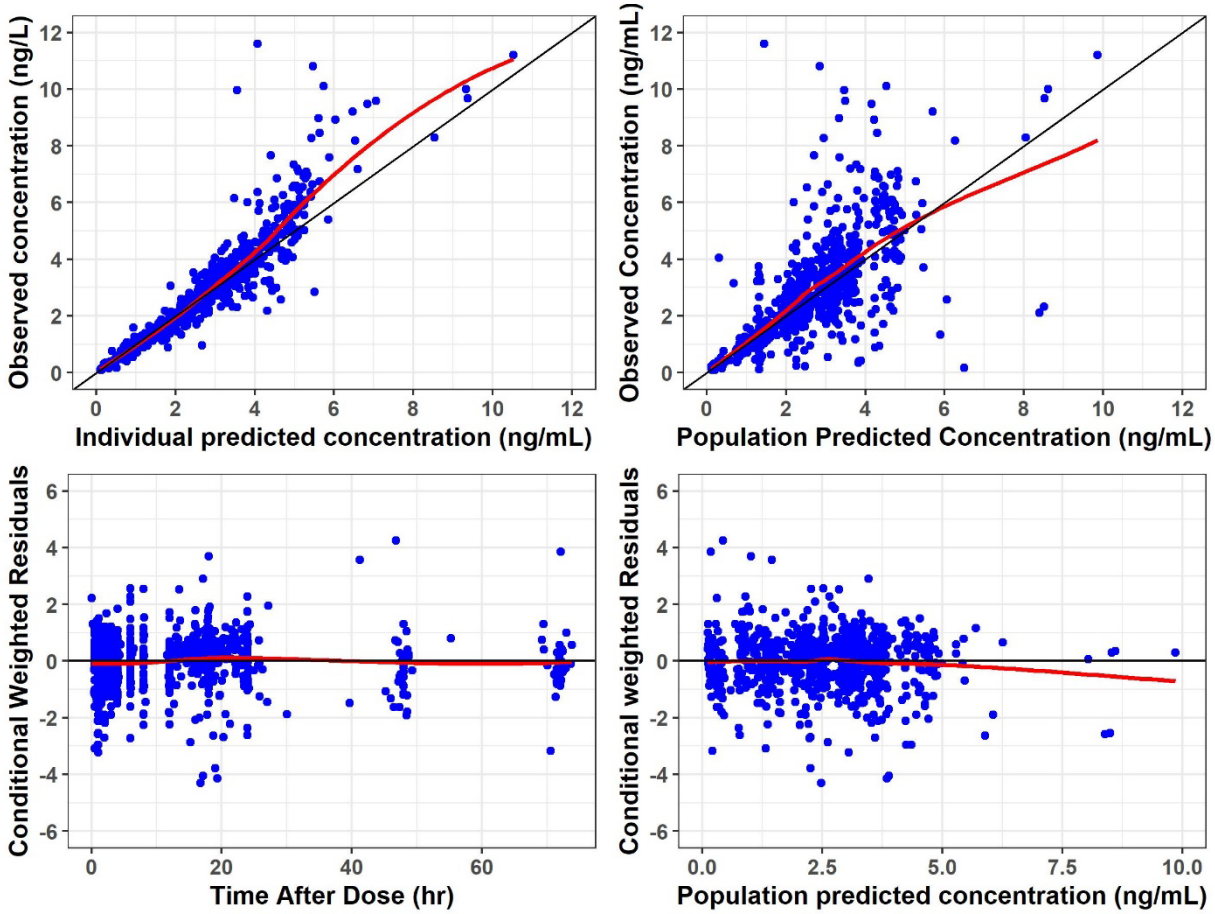
Abbreviations: CL/F=apparent total clearance, Vc/F=apparent volume of central compartment, Vp/F=apparent volume of peripheral compartment, Q/F=inter compartment clearance between central and peripheral compartments, Ka1=first-order absorption before MTIME, Ka2=first-order absorption after MTIME, MTIME=Time point where Ka1 changes to Ka2, F1=relative bioavailability, Hill coefficient: Coefficient associated with the slope of the maturation profile, TM_{50}= Post menstrual age (weeks) when reaching 50% of adult PK parameters, IIV=inter-subject variability, CI=confidence interval, RSE=relative standard error, CV=coefficient of variation, σ^2_{prop}=proportional residual error; BW: body weight.

The reference population is a 70-kg subject ≥2 yr of age.
Covariate relationships:
$CL/F = 21.7 * (WT/70)^{0.75} * PMA^{3.4}/(PMA^{3.4}+47.7^{3.4})$
$Vc/F = 431 * (WT/70)$
$Q/F = 18.4 * (WT/70)^{0.75}$
$Vp/F = 248 \times (WT/70)$

Source: Adapted from population pharmacokinetic analysis report (table 5-3) available at m5.3.3.5-seq 0506. Reviewer's independent analysis provides the similar estimates of model parameters.

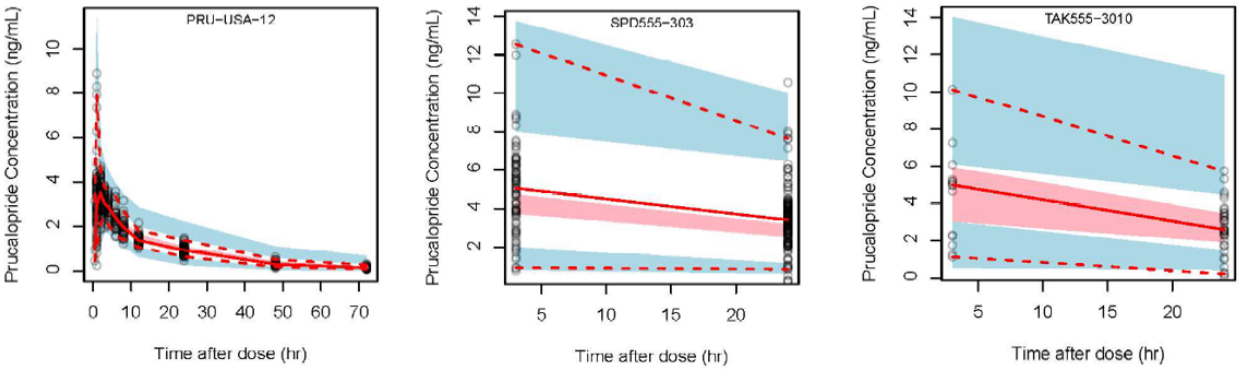
[16] Rhodin MM, et al., Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol, 2009. 24(1): p. 67-76.

Figure 3: Goodness-of-fit Plots for the Final PK Model in Pediatric Subjects with Functional Constipation



Source: Based on the reviewer's model output from final model run

Figure 4: Prediction-Corrected Visual Predictive Check for the Final PK Model in Pediatric Subjects with Functional Constipation



Source: Applicant's PopPK report

Note: Open Circle: Observed Concentrations; Solid Line: Median of Observed Concentrations; Dashed Lines: 2.5th and 97.5th Percentile of Observed Concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 2.5th and 97.5th Percentiles of Predicted Concentrations

Summary of Pharmacokinetics Analyses

The PK model adequately characterized the PK behavior of prucalopride observed in pediatric studies as indicated by goodness of fit and prediction corrected VPC plots. The estimated PK parameter values in the final PopPK model were consistent with those estimated in the previous model of pediatric subjects. The estimated median terminal half-life of prucalopride was 21 hours, which is consistent with the value of 24 hours reported in the approved prucalopride label.

Body weight was identified as a significant predictor of prucalopride PK. Clearance and volume of distribution increased with increasing body weight. For the weight ranges observed in the analysis population (11-110 kg), CL/F ranged from 5.42-30.5 L/hr, indicating that CL/F values ranged from 75% lower to 40% higher compared to the typical CL value (21.7 L/hr) for a subject weighing 70 kg (Table 31).

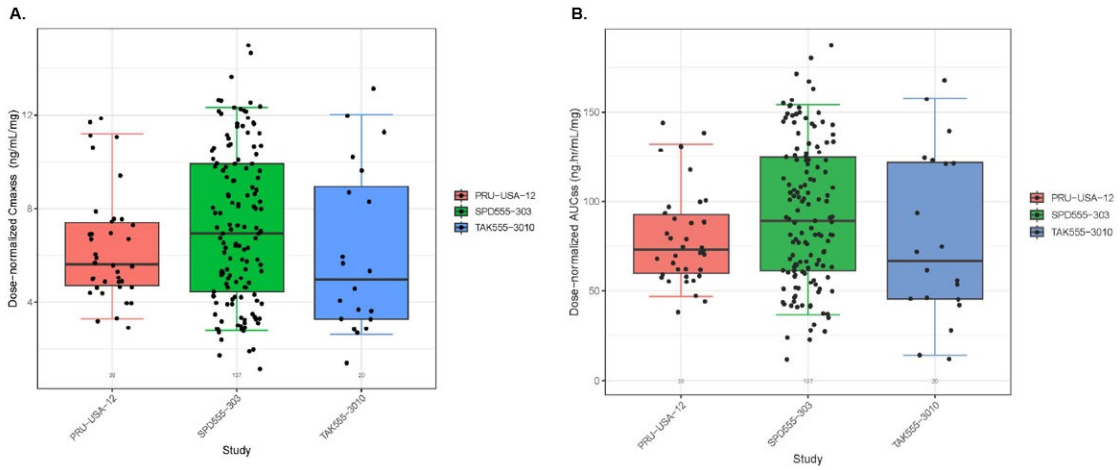
The typical estimates for Vc/F and Vp/F were 431 L and 248 L, respectively. Across the overall analysis population's weight range, Vc/F and Vp/F varied from 67.7-677 L and 39.0-390 L, respectively. These values ranged from 84% lower to 57% higher compared to the typical values for a subject weighing 70 kg (Table 31).

Other covariates such as age, gender, study (Phase 1 vs Phase 3), formulation and eGFR had no significant impact on prucalopride PK. Note that the impact of race couldn’t be evaluated due to lack of data as >90% of subjects were Caucasian/White with very few Black or African American (4%) included in the analysis.

Model Predicted Exposures in Pediatric Subjects

Predicted steady-state exposures (AUCss and Cmax,ss) are generally similar across the three pediatric studies. The 90% prediction interval of dose-normalized, model-predicted exposures at steady-state (Cmax, ss, AUCss) was well aligned across the three pediatric studies, suggesting dose-proportional PK of prucalopride within the dose range evaluated in pediatric subjects (Figure 5).

Figure 5: Predicted Dose-Normalized Exposures (Cmax,ss [A] and AUCss [B]) by Study



Source: The Applicant's PopPK report (pages 64-5) - available at m5.3.3.5-seq 0506
Note: Dose-normalized post-hoc exposures following actual doses. Box presents median (25th and 75th percentiles) and whiskers present 90% CI

However, it is noted that dose-normalized exposures in Study TAK-555-3010 indicated that Cmax,ss and AUCss following the high dose regimen were lower compared to the low dose regimen. It may be attributed to the higher median body weight in the high dose group compared to the low dose group and sparse PK sampling.

On the other hand, the steady-state exposures derived using individual post-hoc PK parameters estimated for all subjects from Study TAK-555-3010 (Table 32, Figure 2B and C in Section 6.3.1) indicate that for the low dose group, the exposures were well within the range of adult reference exposures. For the high dose group, exposures were slightly outside the adult reference range of 2 mg QD but were generally lower than the mean observed exposures following prucalopride 4 mg QD dosing in healthy adult subjects (mean AUCtau: 219 ng.h/mL, mean Cmax: 15.2 ng/mL). The reviewer's analysis on pooled pediatric subjects provided higher predicted values for upper boundary of Cmax,ss and AUCss than that of TAK-555-3010. Nevertheless, the highest concentration simulated for pediatric subjects was far lower than mean PK exposures (Cmax,ss: 87.6 ng/mL and AUCss: 1212 ng.h/mL) associated with maximum tolerated dose, 20 mg QD in adults.

Table 32: Simulated Exposures of Prucalopride at Steady-State in Pediatrics and Reference Exposures in Adults

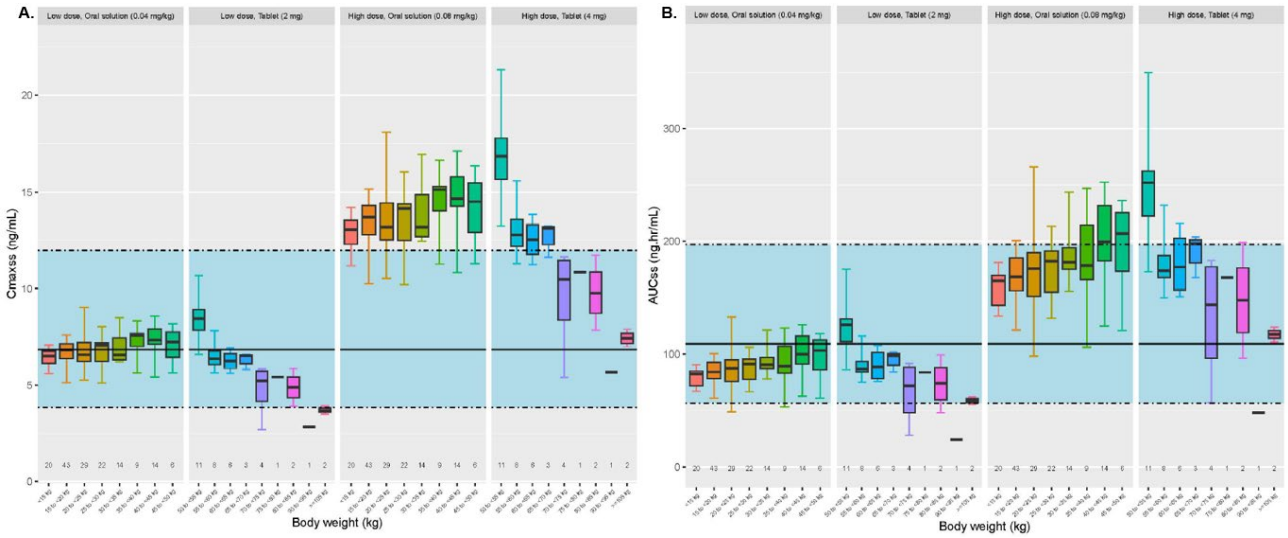
	TAK-555-3010[a]		Pooled pediatric population[b]		Reference population	
PK parameters	Low dose (N=8)	High dose (N=12)	Low dose (N=95)	High dose (N=100)	Adult 2 mg QD[c] (N=1343)	Adult 4 mg QD[d] (N=12)
AUCss (ng.h/mL)	88.5 (75.6 – 157.9)	127 (47.3 – 223.4)	77.6 (37 – 161)	160 (60 – 341.7)	109.3 (56.6 – 197.1)	219 (38)
Cmax,ss (ng/mL)	6.74 (5.2 – 10.0)	10.7 (6.24 – 15.9)	6.2 (3.9 – 10.2)	12.7 (6.7 – 21.75)	6.86 (3.86 – 11.96)	15.2 (2.6)

Source: Reviewer's analysis using the Applicant's PopPK model, updated with PK study results from Study PRU-BEL-15
AUCss: area under the plasma concentration-time curve at steady-state; Cmax,ss: maximum observed plasma concentration at steady-state. Simulated PK parameters include median (90% prediction interval except for adult 4 mg QD. For adult 4 mg QD, mean (SD)

a. PopPK Posthoc PK parameters from the PopPK modeling report
b. Data from pediatric studies TAK-555-3010, SPD555-303, and PRU-USA-12; popPK simulation with TAK-555-3010 dosing regimen
c. Data from 13 studies in adult subjects (phases 1, 2, and 3)
d. Data from Study PRU-BEL-15 that evaluated 4 mg QD for 6 days. Mean (SD) PK parameters are reported

Moreover, following both weight-based dosing in pediatric subjects, the median and the range of exposures increased slightly with increasing body weight for both low and high dose groups. However, for fixed dosing, the trend has been reversed as exposures tended to have decreased with increasing body weight (Figure 6). The exposures for the low dose groups were within the adult exposure range following the recommended dose of 2 mg QD. For the high dose groups the exposures were slightly outside the adult reference range (Figure 6) but were below the mean AUCss and Cmax,ss at the 4 mg QD in healthy adult subjects (Table 32).

Figure 6: Simulated Exposure versus Body weight Plots Following a Low Dose/High Dose Prucalopride Regimen Based on Study TAK-555-3010



Source: Adapted from the Applicant's PopPK report, Figure 5-18
Simulated exposures following low dose and high dose. Blue shaded area: adult 90% prediction interval for AUC (56.6 – 197.1 ng.hr/mL) and Cmax,ss (3.86 – 11.96 ng/mL). Median AUC and Cmax,ss are 109.3 ng.hr/mL and 6.86 ng/mL, respectively

14.5. Additional Clinical Outcome Assessment Analyses

The descriptive results for the CFB in SBM endpoint at Week 12 in subgroups defined by age, number of SBM at baseline and compliance levels are summarized in Table 33.

Table 33: Primary Endpoint: Change from Baseline in Average Number of Weekly SBMs at Week 12 by Subgroup (Part A: Toilet-Trained Participants who were at Least 3 Years of Age) (Modified Intent-to-treat Analysis Set)

	Placebo		Prucalopride Low Dose		Prucalopride High Dose	
	Observed value	Change from baseline	Observed value	Change from baseline	Observed value	Change from baseline
Age						
< 12 years						
n	26	26	25	25	24	24
n*	23	23	17	17	18	18
Mean[a] (SD)	2.9 (1.7)	1.4 (1.8)	3.0 (1.7)	1.6 (2.0)	2.6 (1.6)	1.2 (1.5)
Median[a]	2.3	0.8	2.8	1.6	2.2	0.7
≥ 12 years						
n	15	15	19	19	14	14
n*	13	13	13	13	10	10
Mean[a] (SD)	4.3 (3.8)	3.3 (3.8)	4.4 (2.8)	2.8 (3.1)	2.2 (1.6)	0.9 (1.7)
Median[a]	3	2.3	4	2.5	1.9	0.4
SBM/week, baseline						
≤ 1 SBM/week						
n	24	24	25	25	23	23
n*	22	22	16	16	15	15
Mean[a] (SD)	4 (3.0)	2.8 (3.1)	4 (2.7)	2.9 (2.9)	2.3 (1.1)	1.2 (1.4)
Median[a]	3	2	3.2	2.3	1.8	1
> 1 SBM/week						
n	17	17	19	19	15	15
n*	14	14	14	14	13	13
Mean[a] (SD)	2.5 (1.8)	1.0 (1.8)	3.1 (1.8)	1.3 (1.9)	2.7 (1.9)	0.9 (1.9)
Median[a]	2	0.6	2.9	1.1	2	0.4
Compliance[b]						
< 80%						
n	16	16	26	26	18	18
n*	12	12	13	13	9	9
Mean[a] (SD)	3.8 (3.8)	2.7 (3.8)	3.3 (2.5)	1.9 (2.8)	1.7 (0.8)	0.1 (0.9)
Median[a]	2.6	1.7	2.8	1	1.8	0.4
≥ 80%						
n	25	25	18	18	20	20
n*	24	24	17	17	19	19
Mean[a] (SD)	3.2 (2.0)	1.8 (2.2)	3.8 (2.2)	2.3 (2.4)	2.8 (1.7)	1.5 (1.7)
Median[a]	2.7	0.8	3.5	1.7	2	1

Source: Clinical Study Report Table 11.p (page 103) and Table 11.q (page 104), and Table 2.b from response to information request dated 1/10/25. Verified by reviewer using ADBOWEL.xpt and ADQS.xpt

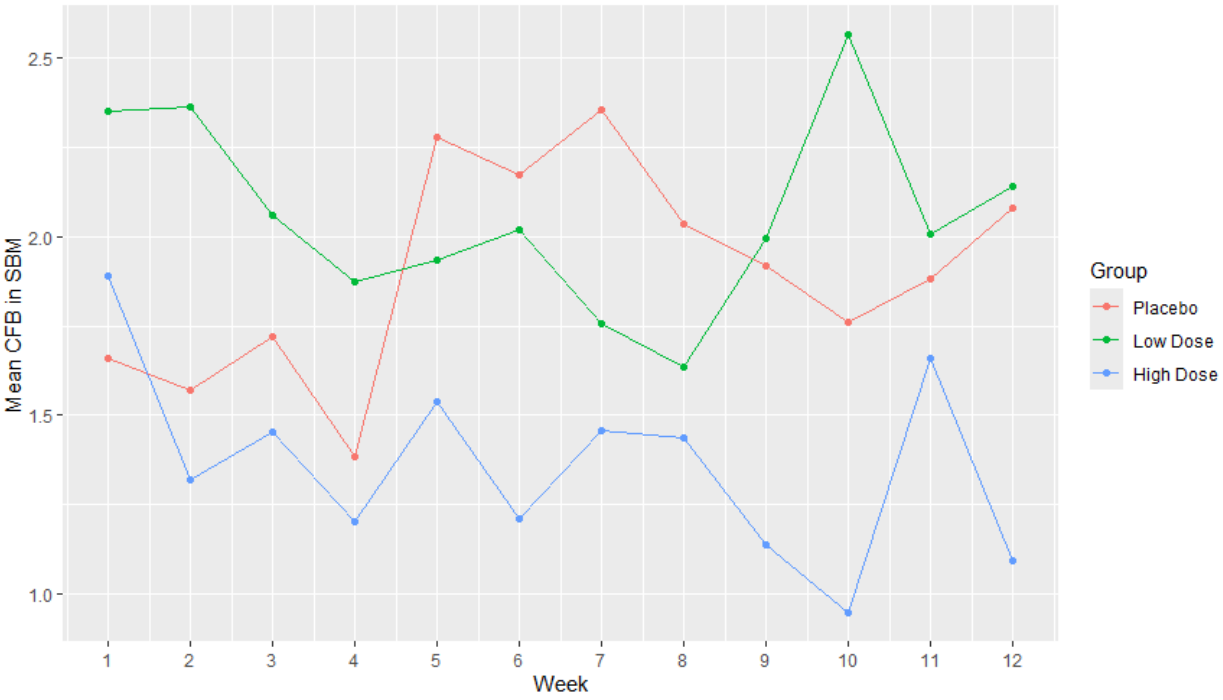
[a] Mean (SD) and median were based on subjects with non-missing measurements

[b] Compliance was calculated as the number of days treatment was taken (based on self-reported diary data) divided by duration of exposure.

Abbreviations: n=number of participants with at least 1 assessment during Week 12; n*=number of participants with a non-missing measurement (i.e., ≥ 4 assessments during Week 12 and the screening period); SBM=spontaneous bowel movement; SD=standard deviation

The mean CFB in SBM throughout the 12 weeks of the trial are described in Figure 7.

Figure 7: Change from Baseline[a] in Average Number of Weekly SBMs over 12 Weeks (Part A: Toilet-Trained Participants who were at Least 3 Years of Age) (Modified Intent-to-treat Analysis Set)



Source: Based on Clinical Study Report Table 11.m (page 98). Verified by reviewer using ADBOWEL.xpt
[a] Mean CFB in SBM was based on subjects with non-missing measurements
Abbreviations: CFB: Change from baseline; SBM: spontaneous bowel movements

14.6. Supplementary Tables

Table 34: Study TAK-555-3010 Recoded Terms

Applicant's AE Code (number of events recoded)	Reviewer's Recoded Term
Abdominal pain lower (2)	Abdominal pain
Abdominal pain upper (6)	Abdominal pain
Electrocardiogram ST segment elevation (1)	Electrocardiogram abnormal
Nasopharyngitis (15)	Upper respiratory tract infection
Viral upper respiratory tract infection (1)	Upper respiratory tract infection
Pharyngitis (1)	Upper respiratory tract infection
Pharyngitis streptococcal (6)	Upper respiratory tract infection
Sinusitis (1)	Upper respiratory tract infection
Nasal congestion (4)	Upper respiratory tract infection

Applicant's AE Code (number of events recoded)	**Reviewer's Recoded Term**
Rhinorrhoea (5)	Upper respiratory tract infection
Otitis media (2)	Ear infection
Platelet count increased (1)	Thrombocytosis
Depressive symptom (2)	Depression
Alanine aminotransferase increased (1)	Hepatic enzyme increased

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Regulatory Project Manager	Kristina Luong	OND/ORO/DROII	Sections: 3.1, 3.2, 14.2	Select one: ☒ Authored ☐ Approved
	Signature: KRISTINA N. LUONG -S			Digitally signed by KRISTINA N. LUONG -S Date: 2025.07.01 10:31:39 -04'00'
Nonclinical Supervisor	Sushanta Chakder	OND/OII/DPTII	Sections: 5	Select one: ☒ Authored ☒ Approved
	Signature: Sushanta K. Chakder -S			Digitally signed by Sushanta K. Chakder -S Date: 2025.07.01 10:38:22 -04'00'
Clinical Pharmacology and Pharmacometrics Reviewer	Selim Fakhruddin	OTS/OCP/DIIP	Section: 6, 14.4	Select one: ☒ Authored ☐ Approved
	Signature: Selim Fakhruddin -S			Digitally signed by Selim Fakhruddin -S Date: 2025.07.01 13:17:55 -04'00'
Clinical Pharmacology Team Leader	Shen Li	OTS/OCP/DIIP	Section: 6, 14.4	Select one: ☐ Authored ☒ Approved
	Signature: Shen Li -S			Digitally signed by Shen Li -S Date: 2025.07.01 13:33:40 -04'00'
Pharmacometrics Team Leader	Jiang Liu	OTS/OCP/DPM	Section: 6, 14.4.2	Select one: ☐ Authored ☒ Approved
	Signature: JIANG LIU -S			Digitally signed by JIANG LIU -S Date: 2025.07.01 15:03:35 -04'00'

Statistical Reviewer	Joshua Sampson	OTS/OB/DBIII	Sections: 1.2, 1.3, 8.1, 8.3	**Select one:** ☒ Authored ☒ Approved
	Signature: JOSHUA N. SAMPSON -S Digitally signed by JOSHUA N. SAMPSON -S Date: 2025.07.01 15:37:30 -04'00'			
Statistical Team Leader	Paul Imbriano	OTS/OB/DBIII	Sections: 1.2, 1.3, 8.1, 8.3	**Select one:** ☐ Authored ☒ Approved
	Signature: PAUL M. IMBRIANO -S Digitally signed by PAUL M. IMBRIANO -S Date: 2025.07.02 08:33:25 -04'00'			
Clinical Reviewer	Irena Lavine	OND/OII/DG	Sections: 1, 2, 3.3, 4.1, 7, 8, 10, 11, 13, 14.2, 14.6	**Select one:** ☒ Authored ☐ Approved
	Signature: Irena G. Lavine -S Digitally signed by Irena G. Lavine -S Date: 2025.07.02 13:05:29 -04'00'			
Cross Discipline Team Leader; Associate Director for Labeling	Joette Meyer	OND/OII/DG	Approved All Sections	**Select one:** ☐ Authored ☒ Approved All
	Signature: Joette M. Meyer -S Digitally signed by Joette M. Meyer -S Date: 2025.07.02 15:19:52 -04'00'			
Division Director (Signatory)	Jessica J. Lee	OND/OII/DG	Approved All Sections	**Select one:** ☐ Authored ☒ Approved All Sections
	Signature: JESSICA J. LEE -S Digitally signed by JESSICA J. LEE -S Date: 2025.07.03 09:57:42 -04'00'			

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/s/

JOETTE M MEYER
07/10/2025 08:36:06 AM