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SCIENCE MEDICINES HEALTH

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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Resolor

(prucalopride)

Procedure no: EMEA/H/C/001012/P46/023

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	27 May 2024	27 May 2024	☐
☐	CHMP Rapporteur Assessment Report	01 July 2024	01 July 2024	☐
☐	CHMP members comments	15 July 2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	18 July 2024	n/a	☐
☒	CHMP adoption of conclusions:	25 July 2024	25 July 2024	☐

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1. Introduction

On 9th May 2024, the MAH submitted a completed paediatric study for Resolor in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that 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 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The product Resolor is a film coated tablet containing the active ingredient prucalopride. Resolor is only indicated for adults. In this study prucalopride was provided as an oral solution (for participants weighing <50 kg) or as a tablet (for participants weighing ≥50 kg).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

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.

2.3.2. Clinical study

Description
TAK-555-3010 was 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 male and female pediatric and adolescent participants with functional constipation as defined by the modified Rome IV criteria for child/adolescent FGID. This TAK-555-3010 pediatric study was designed to fulfill the US Pediatric Research and Equity Act requirement and 2 postmarketing requirements, PMR 3529-1 and PMR 3529-6 for Motegrity New Drug Application 210166.

The study was initiated on 13 July 2021 (first participant enrolled). The study started with a 10 to 33-day screening period, including a disimpaction for all participants, 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.

Methods

Study participants

In Part A, a total of 175 participants were randomized in a 1:1:1 ratio to the prucalopride lowdose group (N=60), prucalopride -highdose group (N=59), or matching placebo (N=56). A total of 134 (76.6%) participants completed Part A; 41 (23.4%) participants discontinued the study and the study drug. Main reasons for study and study drug discontinuation were withdrawal of consent by participant (17 [9.7%] participants) and lost to followup- (9 [5.1%] participants).

Following completion of Part A, participants on placebo were rerandomized to prucalopride low- or high-dose in a 1:1 ratio; participants on prucalopride in Part A remained on the same dose in Part B. A total of 65 (48.5%) participants completed Part B and thus, the study; 67 (50.0%) participants discontinued the study and the study drug. Main reasons for study and study drug discontinuation were study terminated by sponsor (35 [26.1%] participants), withdrawal of consent by participant (12 [9.0%] participants), and reasons listed as "other" (13 [9.7%] participants).

In Part A, 91 (52.0%) participants were female, and 84 (48.0%) participants were male. The mean (SD) age was 9.7 (3.88) years. Most participants (106 [60.6%]) were ages ≥3 and <12 years. Participants had a mean (SD) time since diagnosis of constipation of 3.84 (3.511) years. All participants had fecal disimpaction during screening.

In the subgroup of participants who proceeded to Part B, 68 (50.7%) participants were female and 66 (49.3%) participants were male. The mean (SD) age was 9.8 (3.83) years. Most participants (80 [59.7%]) were ages ≥3 and <12 years. Participants had a mean (SD) time since diagnosis of constipation of 3.82 (3.540) years. All participants had fecal disimpaction during screening.

Treatments

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

Objective(s)

The primary objectives were:

• To evaluate the efficacy of prucalopride during the 12-week double-blind, placebo-controlled treatment phase in toilet-trained participants with functional constipation who were at least 3 years of age.

• To evaluate the long-term (48 weeks) safety and tolerability of prucalopride in toilet-trained participants with functional constipation who were at least 3 years of age.

The key secondary objective was:

• To evaluate the efficacy of prucalopride on signs and symptoms of functional constipation (stool consistency, straining, and stool frequency responder index), during the 12-week double-blind, placebo-controlled treatment phase in toilet-trained participants with functional constipation who were at least 3 years of age.

Other secondary objectives were:

• To evaluate the effect of prucalopride on the frequency of fecal incontinence.

• To evaluate safety and tolerability of prucalopride over 12 weeks of treatment in toilet-trained participants who were at least 3 years of age.

• To evaluate the PK of prucalopride by combining sparse PK blood sampling that was conducted during

the 12-week double-blind, placebo-controlled phase together with the data from previous pediatric studies for further population PK (popPK) analysis (separate reporting).

Outcomes/endpoints
Primary endpoint:
• The average CFB in number of SBMs5 per week derived from the (e-Diary) data over 12 weeks, collected during the placebo-controlled part (Part A).

Key secondary endpoints (efficacy):
– The average CFB in stool consistency (based on BSFS score), assessed as the weekly average during the 12-week double-blind, placebo-controlled treatment phase.
– The average CFB in straining (based on a 3-point Likert scale), assessed as the weekly average during the 12-week double-blind, placebo-controlled treatment phase.
– The proportion of responders with a responder 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.

Other secondary endpoint (efficacy):
– Proportion of participants with fecal incontinence per week during the 12-week treatment period.

Safety endpoint:
– The proportion of participants with TEAEs (serious, non-serious, related, non-related) and the proportion of participants with clinically relevant laboratory test abnormalities, ECG findings, vital signs findings, or new findings in physical examination over 12 and 48 weeks of treatment.

Sample size
The sample size was estimated through statistical simulations based on the Hochberg step-up procedure to control the type I error rate for primary efficacy endpoint. These simulations showed that with 80 toilet-trained participants who were at least 3 years of age per treatment arm, Part A of the study would have at least 90% power to detect a treatment difference of 1.40 in primary efficacy endpoint between at least one active dose vs placebo assuming pooled SD of 2.5, using a 2-sided 2-sample t-test at a significance level of 5% based on the Hochberg step-up procedure to control the type I error rate for primary efficacy endpoint.

Randomisation and blinding (masking)
Following initial randomization, participants entered the 12-week placebo-controlled part (Part A) where they received either prucalopride at a low dose, prucalopride at a high dose, or placebo. Upon completion of the placebo-controlled part (Part A), all participants who were on placebo in the placebo-controlled part (Part A) were rerandomized into the safety extension part (Part B) where they received prucalopride at either a low dose or a high dose

Matching placebo solution/tablets were available such that the blinding could be assured in identical packaging. The participants, investigator, study coordinator, sponsor, and the entire study processing team remained blinded to the treatment assignment. The set-up of the randomization system ensured that the blind was maintained and did not reveal treatment allocation to any unauthorized personnel.

Statistical Methods
Futility evaluation was based on the conditional power (Lan and Wittes 1988) using a stopping threshold of 20% for each dose arm.

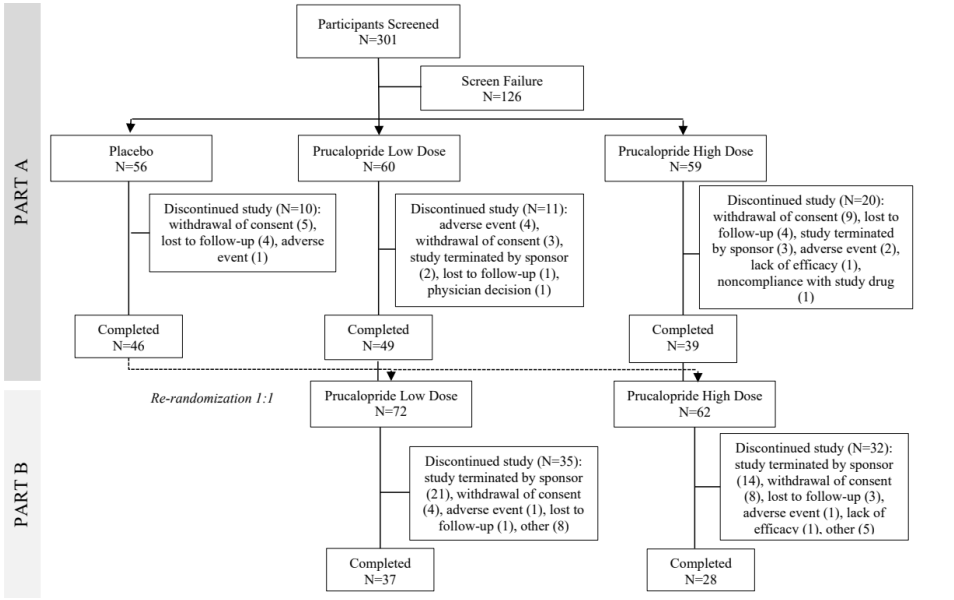
Both low-dose and high-dose comparisons with placebo based on the primary endpoint had a conditional power (probability) of less than 20%. Therefore, the study was stopped for futility.

No further inferential efficacy analysis was conducted since the original power calculation was based on 240 participants (80 per each arm of placebo, low dose, and high dose) who should have either completed or withdrawn from Part A.

Primary and secondary efficacy endpoints were reported in a descriptive manner.

Results

Participant flow



Efficacy results

Primary endpoint

The mean change from baseline to Week 12 in weekly SBMs was similar in the prucalopride low-dose and placebo groups (+2.1 SBMs for both groups) and lower in the prucalopride high-dose group (+1.1 SBM) (Table 1).

Table 1: Change from Baseline in Average Number of Weekly SBMs at Week 12 (Part A) (Modified Intent-to-treat Analysis Set)

	Placebo (N=52)		Prucalopride Low Dose (N=56)		Prucalopride High Dose (N=55)	
Timepoint Statistic	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 (SD)	3.4 (2.68)	2.1 (2.80)	3.6 (2.30)	2.1 (2.53)	2.5 (1.54)	1.1 (1.59)
Median	2.6	1.3	3.0	1.6	2.0	0.5
Min, max	0, 14	-2, 13	0, 10	-2, 9	0, 7	-1, 5

BM: bowel movement; max: maximum; min: minimum; N: number of participants in population treatment group; n: number of participants with assessment; n*: number of participants with average; SBM: spontaneous bowel movement; SD: standard deviation.

Notes: A BM was 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.

Baseline for daily diary data was defined as the average value over all diary days observed prior to taking the first dose of study drug, excluding the disimpaction period.

For the calculation of average weekly number of SBM, it was required that there were at least 4 days with completed diary data, otherwise the average weekly number of SBM was set to missing.

The average number of SBM per week was calculated as (7*SBMs/week)/(number of days with observation).

Change from baseline was calculated as the average number of SBMs minus the average number of SBMs at baseline.

The modified intent-to-treat analysis set includes all randomized participants who received at least 1 dose of study drug in Part A.

Table includes data with an assessment date from date of first dose of Part A study drug through last dose of Part A study drug.

An increase in weekly SMBs was observed as early as Week 1 and maintained throughout Part A in both prucalopride dose groups; this early increase was also observed in the placebo group.

Sensitivity analysis results confirmed results observed in the main analysis of the primary endpoint:

- Using the completers analysis set, mean change from baseline in SBMs at Week 12 was +1.9 in the prucalopride low-dose group, +0.9 in the prucalopride high-dose group, and +1.4 in the placebo group. An increase in SBMs was observed as early as Week 1 and maintained throughout Part A in all 3 treatment groups.
- Using the per protocol analysis set, mean change from baseline in SBMs at Week 12 was +1.7 in the prucalopride low-dose group, +1.4 in the prucalopride high-dose group, and +1.5 in the placebo group. An increase in SBMs was observed as early as Week 1 and maintained throughout Part A in all 3 treatment groups.

Subgroup analysis:

- In the subgroup of toilet-trained participants aged <12 years, mean change from baseline in SBMs at Week 12 was 1.6 in the prucalopride low-dose group, 1.2 in the prucalopride high-dose group, and 1.4 in the placebo group. An increase in SBMs was observed at Week 1 and maintained throughout Part A in all 3 treatment groups.
- In the subgroup of toilet-trained participants aged 12 to 17 years, mean change from baseline in SBMs at Week 12 was 2.8 in the prucalopride low-dose group, 0.9 in the prucalopride high-dose group, and 3.3 in the placebo group. An increase in SBMs was observed at Week 1 and maintained throughout Part A in all 3 treatment groups.

Secondary endpoints

Stool Consistency

In toilet-trained participants aged <8 years, for whom the BSFS score was recorded by the caregiver, mean change from baseline in stool consistency at Week 12 was +9.8 in the prucalopride low dose group, +7.1 in the prucalopride high dose group, and -0.1 in the placebo group.

In toilet-trained participants aged ≥8 years, who self-reported their BSFS, mean change from baseline in stool consistency at Week 12 was +13.1 in the prucalopride low dose group, +7.0 in the prucalopride high dose group, and +12.6 in the placebo group.

Straining

In toilet-trained participants for whom the 3-point Likert straining score was recorded by the caregiver, mean change from baseline in straining at Week 12 was -5.2 in the prucalopride low-dose group, -7.6 in the prucalopride high-dose group, and -5.7 in the placebo group.

Proportion of Responders

Two (3.6%) participants in the prucalopride low-dose group and 1 (1.9%) participant in the placebo group met the criteria and were defined as responders.

Fecal Incontinence

One (3.0%) participant in the prucalopride low-dose group, 5 (16.7%) participants in the prucalopride high-dose group, and 4 (12.9%) participants in the placebo group had experienced fecal incontinence by Week 12.

Safety results

In Part A, participants were exposed to study drug for a mean (SD) of 74.2 (24.69) days, and in Part B, participants were exposed to study drug for a mean (SD) of 192.9 (87.15) days.

In Part A, TEAEs occurred in 24 (40.0%) participants in the prucalopride low-dose group, 18 (30.5%) participants in the prucalopride high-dose group, and 15 (26.8%) participants in the placebo group.

In Part B, TEAEs occurred in 22 (30.6%) participants in the prucalopride low-dose group and 17 (27.4%) participants in the prucalopride high-dose group.

The most frequently reported TEAEs (occurring in ≥5% of participants in any treatment group) were:
• In Part A: headache (8 participants [13.3%] in the prucalopride low dose group, 5 participants [8.5%] in the prucalopride high dose group, and 3 participants [5.4%] in the placebo group), vomiting (8 participants [13.3%], 4 participants [6.8%], and 2 participants [3.6%], respectively), abdominal pain and nasopharyngitis (3 participants [5.0%], 1 participant [1.7%], and 1 participant [1.8%], respectively, each).
• In Part B: headache (3 participants [4.2%] in the prucalopride low dose group and 5 participants [8.1%] in the prucalopride high dose group), nasopharyngitis (7 participants [9.7%] and 1 participant [1.6%], respectively).

The most frequently reported TEAEs considered related to the study drug by the investigator (occurring in ≥5% of participants in any treatment group) were:
• In Part A: headache (4 participants [6.7%] in the prucalopride high dose group, 3 participants [5.1%] in the prucalopride low dose group, and no participants in the placebo group) and vomiting (5

participants [8.3%], no participants, and 1 participant [1.8%], respectively).
• In Part B, none of the related TEAEs occurred in more than 1 participant per prucalopride dose group.

Most TEAEs were mild or moderate in intensity.

Severe TEAEs were reported as follows:
• In Part A, 1 participant (1.7%) in the prucalopride high dose group had a severe TEAE of hand fracture. None of the participants in the prucalopride low dose or placebo groups had severe TEAEs.
• In Part B, 1 participant in the prucalopride low dose group had a severe TEAE of abdominal pain and 2 participants (3.2%) in the prucalopride high dose group had severe TEAEs of abdominal pain and fecaloma. In addition, 1 participant had 3 TEAEs of special interest during the study. This participant, who was randomized to the placebo group in Part A and re-randomized to the prucalopride low dose group during Part B, experienced a TEAE of depression during Part A (while on placebo) and TEAEs of intentional self-injury and suicidal ideation during Part B. All 3 TEAEs were considered serious and unrelated to the study drug by the investigator.

No deaths were reported during the study.

2.3.3. Discussion on clinical aspects

This study included pediatric subjects, between 3-17 years old with functional constipation. They were randomised into a low- or a high-dose of prucalopride or a placebo group. Part A of the study was for 12 weeks, followed by a 36 weeks safety extension, Part B.

An interim analysis was performed when 50% of the participants were randomised into the study and had completed part A. The purpose was to compare the efficacy of both prucalopride doses with placebo and decide to continue or stop the study for futility. After the futility analysis based on conditional power and using a stopping threshold of 20% for each dose arm, the study was stopped for futility. All efficacy endpoints, including primary, secondary, and exploratory endpoints, were therefore reported in a descriptive manner. In the randomized, double-blind comparison (Part A), an improvement in the number of SBMs was observed in all treatment groups, including placebo, at Weeks 1 and 2, and only small differences were observed between prucalopride low dose, prucalopride high dose, and placebo in the number of SBMs per week derived from the e-Diary data over 12 weeks.

A previous study in the pediatric population could also not demonstrate efficacy of prucalopride in this patient group.

The safety results were in line with the known safety profile for prucalopride and no new safety concerns were identified.

3. Rapporteur’s CHMP overall conclusion and recommendation

The efficacy of prucalopride in pediatric subjects with functional constipation could not be demonstrated and the study was terminated for futility after an interim analysis and a futility analysis when 50% of the participants were randomised into the study and had completed part A. This result is in line with information already included in section 5.1 of the SmPC for Resolor.

The safety results were in line with the known safety profile for prucalopride without any new safety concerns.

No changes to the SmPC for Resolor is proposed and the benefit-risk profile remain unchanged.

☒ **Fulfilled:**

No regulatory action required.