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Human Medicines Division

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

Litfulo

Ritlecitinib

Procedure no: EMEA/H/C/006025/P46/006

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	26 Feb 2024	26 Feb 2024	☐
☐	CHMP Rapporteur Assessment Report	02 Apr 2024	03 Apr 2024	☐
☐	CHMP members comments	15 Apr 2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	18 Apr 2024	n/a	☐
☐	CHMP adoption of conclusions:	25 Apr 2024	25 Apr 2024	☐
☐	Submission	07 May 2024	02 May 2024	☐
☐	Re-start	08 May 2024	08 May 2024	☐
☐	CHMP Rapporteur Assessment Report	15 May 2024	15 May 2024	☐
☐	CHMP members comments	21 May 2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	23 May 2024	n/a	☐
☒	CHMP adoption of conclusions:	30 May 2024	30 May 2024	☐

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1. Introduction

On 16 February 2024, the MAH submitted a completed paediatric study for Litfulo, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study B7981031 titled "An interventional PK, PD, Phase 1, open-label study to investigate PK and PD of multiple-dose ritlecitinib in children 6 to less than 12 years of age with severe alopecia areata" is a stand-alone study and also part of a clinical development program. A line listing of all the concerned studies was provided by the MAH.

2.2. Information on the pharmaceutical formulation used in the study

The ritlecitinib formulation used in study B7981031 was 20 mg capsules. For administration, the capsules were dissolved in water and the contents of the capsule in water were taken.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- study B7981031 titled "An interventional PK, PD, Phase 1, open-label study to investigate PK and PD of multiple-dose ritlecitinib in children 6 to less than 12 years of age with severe alopecia areata".

2.3.2. Clinical study

Clinical study number B7981031, An interventional PK, PD, Phase 1, open-label study to investigate PK and PD of multiple-dose ritlecitinib in children 6 to less than 12 years of age with severe alopecia areata.

Description

Study B7981031 was a single-group, uncontrolled, open-label, interventional PK, PD study to estimate the systemic exposures of 20 mg QD of ritlecitinib in at least 12 children with alopecia areata (AA), 6 to less than 12 years of age, including at least 4 participants 6 to less than 9 years of age.

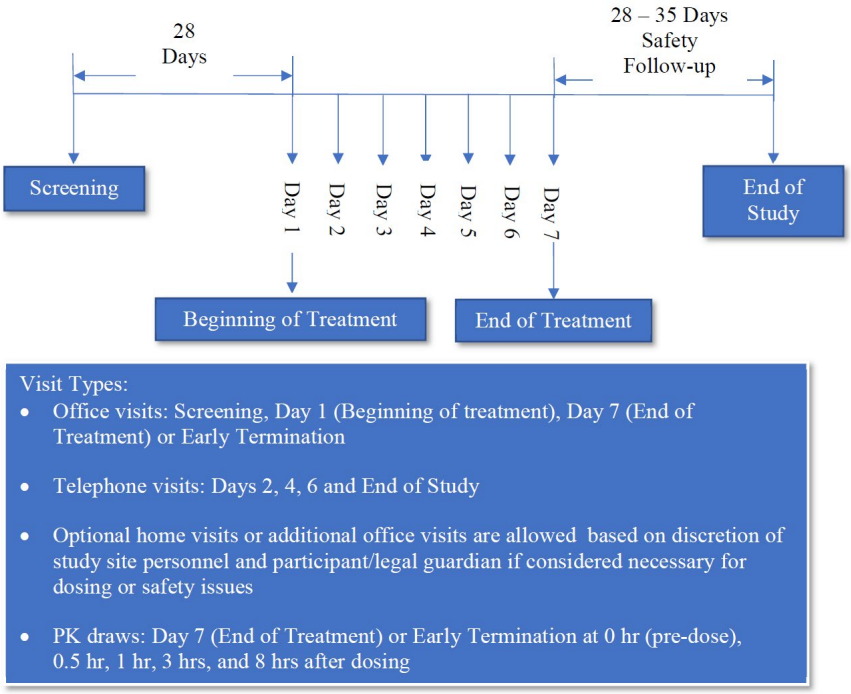
The PK and PD assessments from this study are used for dose selection in subsequent paediatric studies.

Methods

Participants were planned to be screened and, if all eligibility criteria were met, to receive the first dose of study intervention within 28 days after the screening visit. Participants were planned to receive 20 mg ritlecitinib once daily in one dose for 7 consecutive days. On Day 7 (EOT) blood samples for PK were planned to be collected at 0 hr (pre-dose), 0.5 hr, 1 hr, 3 hrs, and 8 hrs after dosing. At least 12

evaluable participants with respect to the primary endpoint were planned to be enrolled in the study. Participants that were not able to provide a full set of evaluable PK data or missed more than 1 dose could be replaced at the discretion of the sponsor. A follow-up visit was planned to be conducted by phone 28 to 35 days after the last dose of ritlecitinib (Refer to Figure 1).

Figure 1. Study scheme



The following ritlecitinib PK parameters were calculated for each participant using NCA analysis of concentration-time data. PK parameters are described in Table 1. Samples below the LLOQ were set to 0 ng/mL for analysis. Actual sample collection times were used for the PK analysis.

Plasma samples were analysed for ritlecitinib by a validated analytical method.

Table 1. Pharmacokinetic parameters determined in protocol B7981031

Parameter	Definition	Method of Determination
AUC_{24}	Area under the plasma concentration time profile over the dosing interval 24 hrs, at steady-state	Linear/Log trapezoidal method
C_{max}	Maximum observed concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$ [a]	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.
CL/F	Apparent clearance	Dose/AUC_{24} after oral dose
V_z/F [a]	Apparent volume of distribution	Dose/(AUC_{24}*k_{el}) after oral dose

a. If data permitted
Pharmacokinetic parameter values were calculated using an internally validated software system, oNCA (version 2.7.8).

The following supporting data from the estimation of t½ were also reported: kel, kel,t(lo), kel,t(hi), and kel,t(n); r2; and the percent of AUCinf, obtained by forward extrapolation ($AUC_{extrap\%}$). Unless otherwise noted, parameters marked if data permitted were reported only where a well-characterised

terminal phase was observed. A well-characterised terminal phase is defined as one with at least 3 data points, r2 ≥0.9 and $AUC_{extrap\%}$ ≥20%.

Study participants

Enrolled in this study were 6 to less than 12-year-old children with a diagnosis of severe AA, including AT and AU, with ≥50% scalp hair loss due to AA (ie, a SALT score of ≥50) at both the Screening and Baseline visits, without evidence of terminal hair regrowth within the previous 12 months.

Treatments

The study intervention was ritlecitinib capsules dissolved in water. The first dose was administered at the study site, in presence of the investigator or designee.

The daily oral dose was 20 mg and the treatment lasted up to 7 days.

The study included a screening period of up to 28 days, a 7-day interventional period, and a 28-35 day follow-up period. The duration of study participation for each participant was approximately 9-10 weeks.

Each site received an initial shipment with enough study intervention for 2 participants. Replacements were provided to the study site as the initial supply was used or expired.

The manufacturing lot number for the study intervention dispensed in this study is provided in Table 2.

Table 2. Study intervention administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/ Potency	Dosage Form
Ritlecitinib Tosylate 20 mg Size 2 Light Gray/Gray Hypromellose Capsule	NA	22-DP-01117	20 mg	Capsule

Objective(s) and outcomes/endpoints

The study objectives and endpoints of study B7981031 are presented in Table 3.

Table 3. Study objectives and endpoints

Type	Objective	Endpoints
Primary		
PK	• To characterize the PK of ritlecitinib in children with AA 6 to less than 12 years of age.	• AUC_{24} on Day 7
Secondary:		
PK	• To further characterize the PK of ritlecitinib in children with AA 6 to less than 12 years of age.	• C_{max}, T_{max}, CL/F, V_Z/F and $t_{½}$ on Day 7
PD	• To characterize the PD of ritlecitinib in children with AA 6 to less than 12 years of age.	• Change from baseline in interferon gamma IP-10 and lymphocyte subsets (T cell, B cell, and NK cells) on Day 7
Safety	• To evaluate the safety and tolerability of ritlecitinib in children with AA 6 to less than 12 years of age.	• TEAE • Treatment related AEs • SAEs and AEs leading to discontinuation • Clinically significant abnormalities in vital signs • Clinically significant abnormalities in clinical laboratory values
Taste assessment	• To assess the overall palatability, acceptability, and tolerability of the proposed age appropriate formulation in children with AA aged 6 to less than 12 years of age.	• Taste assessment

Sample size

A sample size of 12 participants was expected to provide adequate PK information.

Randomisation and blinding (masking)

Allocation:

The investigator's knowledge of the treatment assignment had to not influence the decision to enroll a particular participant or affect the order in which participants were enrolled. Given the small number of participants and the nature of the study (PK, PD) it was very unlikely that the investigator decisions may be affected by bias.

Blinding:

This was an open-label study.

Statistical Methods

The plasma PK parameters were listed and summarised descriptively by nominal PK sampling time. Individual participant and median profiles of the plasma concentration-time data were plotted using actual and nominal times, respectively. Median profiles were presented on both linear-linear and log-linear scales.

Taste acceptability assessment questionnaire was included; results were listed and summarised descriptively (frequencies and percentages).

No statistical hypothesis were tested in this study.

Results

Participant flow

A total of 16 participants were screened and 15 of them were assigned to study intervention, enrolled at 6 centers in the US (see Table 4). Except for 1 participant who discontinued from the study intervention after 2 days of oral administration of ritlecitinib 20 mg QD due to an AE of urticaria on Day 3, all other 14 participants received ritlecitinib 20 mg QD from Day 1 to Day 7. All enrolled participants (n = 15) completed the follow-up.

Table 4. Participant evaluation groups - All participant (protocol B7981031)

	Ritlecitinib 20 mg QD (N=15) n (%)
Screened: 16	
Screened Failure: 1	
Not Screen Failure but not Randomized: 0	
Assigned to Treatment	15 (100.0)
Treated	15 (100.0)
Not Treated	0
Safety Analysis Set	15 (100.0)
PK Concentration Analysis Set	13 (86.7)
PK Parameter Analysis Set	13 (86.7)
PD Parameter Analysis Set	15 (100.0)

Table 5. Disposition events summary - Safety analysis set (protocol B7981031)

Number (%) of Participants	Ritlecitinib 20 mg QD (N=15) n (%)
Disposition Phase: Open Label Treatment	
Participants Entered:	15 (100.0)
Discontinued	1 (6.7)
Reason for Discontinuation	
Adverse Event	1 (6.7)
Completed	14 (93.3)
Disposition Phase: Follow-up	
Participants Entered:	15 (100.0)
Discontinued	0
Reason for Discontinuation	
Adverse Event	0
Completed	15 (100.0)

Recruitment

Number analysed

All enrolled participants (n=15) were included in the safety and PD parameter analysis sets.

A total of 13 participants were included in the PK concentration analysis set and PK parameter analysis set. Two participants were excluded as they had no evaluable PK data (one of them discontinued from study intervention on Day 3 and the other one had the important protocol deviation of PK samples not collected on Day 7).

Baseline data

Demographic characteristics and physical measurements of 15 enrolled participants in this study are summarised in Table 6 and Table 7, respectively. Twelve (80%) participants were female. The median (range) of age (years) was 8.0 (6,11). The majority of the enrolled participants were White (13 participants, 86.7%) and around half of the enrolled participants were Hispanic or Latino (8 participants, 53.3%). The median (range) of the BMI (kg/m2) was 17.06 (13.09, 22.31).

Table 6. Demographic characteristics - Enrolled population (protocol B7981031)

	Ritlecitinib 20 mg QD (N=15)
Age (Years)	
6-8	9 (60.0)
9-11	6 (40.0)
Median (range)	8.0 (6, 11)
Mean(SD)	8.5 (1.60)
(Q1,Q3)	(8, 9)
Gender	
Male	3 (20.0)
Female	12 (80.0)
Race	
White	13 (86.7)
Black or African American	2 (13.3)
Ethnicity	
Hispanic or Latino	8 (53.3)
Not Hispanic or Latino	7 (46.7)

Table 7. Physical measurements at baseline - Safety analysis set (protocol B7981031)

Parameter		Ritlecitinib 20 mg QD (N=15)
Weight (kg)	n	15
	Mean (SD)	32.31 (8.299)
	Median (range)	33.40 (21.00, 50.60)
Height (cm)	n	15
	Mean (SD)	135.23 (9.164)
	Median (range)	137.16 (120.30, 151.50)
Body Mass Index (kg/m^2)	n	15
	Mean (SD)	17.40 (2.730)
	Median (range)	17.06 (13.09, 22.31)

Body Mass Index (kg/m^2) = weight (kg) / [height (cm) × 0.01]^2.
The baseline measurement is the latest measurement during the Screening period.

Prior and concomitant therapy

A total of 5 participants had concomitant medications (iron supplement, dexmethylphenidate (2x), fexofenadine, levothyroxine) during this study and one of them took medications to treat an AE of urticaria.

Exposure and study intervention compliance

One participant received ritlecitinib 20 mg QD at day 1 and day 2 only; all other 14 participants received ritlecitinib 20 mg QD from Day 1 to Day 7. The first and last dose were administered at the study site and doses 2 through 6 were taken at home.

No important protocol deviations related to study intervention compliance were reported in this study.

Two occurrences of the NSAE vomiting were experienced by a participant on Day 6 (no exact time was collected), and it is unknown if the vomiting occurred within 1 hour after the administration of study intervention. As only PK data are used at day 7 to support the popPK model, and there is no accumulation of ritlecitinib, this would not impact the pharmacokinetics.

Pharmacodynamics results

Baseline and change from baseline at day 7 in CD19+ B cells, CD4+ T cells, CD8+ T cells and CD3-CD16+CD56+ NK cells are presented in Table 8.

Table 8. Lymphocyte subsets at baseline and change from baseline at day 7

	Absolute number of cells		**Percentage**	
	Baseline	**Change at day 7**	**Baseline**	**Change at day 7**
B cells median (range)	439.0 (191.0, 881.0) 10^6/L	-19.0 (-116.0, 766.0) 10^6/L	17.0 (10.0, 30.0)	0.5 (-4.0, 5.0)
CD4+ T cells	1.0 (0.6, 1.6) 10^9/L	-0.1 (-0.6, 1.1) 10^9/L	43.0 (28.0, 50.0)	0.0 (-12.0, 11.0)
CD8+ T cells median (range)	0.6 (0.2, 1.5) 10^9/L	0.0 (-0.6, 0.8) 10^9/L	23.0 (14.0, 36.0)	0.5 (-2.0, 5.0)
NK cells median (range)	254.0 (85.0, 729.0)	-25.5 (-318.0, 627.0) 10^6/L	10.0 (5.0, 19.0)	-1.0 (-8.0, 16.0)

Levels of change for total (CD3+) T cells were minimal, similar to the CD4+ and CD8+ subsets of T cells.

Baseline IP-10 and Change from Baseline in IP-10:

- C-X-C Motif Chemokine Ligand 10 (interferon gamma-induced protein 10; IP-10) (pg/mL): The median (range) at baseline was 121.0 (74.7, 888.0) and median (range) change from baseline on Day 7 was -9.9 (-555.0, 104.0).

Pharmacokinetic results

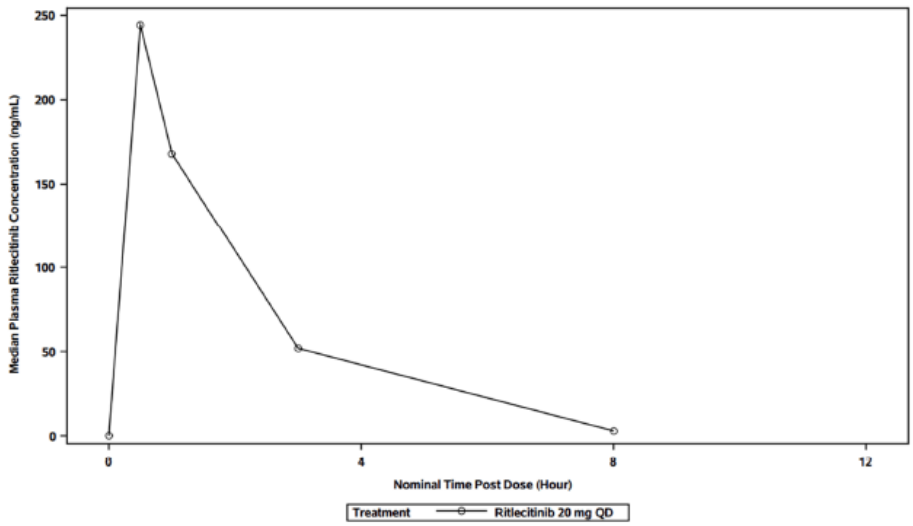
The PK variables and the plasma concentration-time curve are shown in Table 9 and Figure 2.

Table 9. Summary of plasma ritlecitinib - PK parameter analysis set (protocol B7981031)

Parameter, Unit[a]	Ritlecitinib 20 mg QD (N=13)
N2, N3	13, 8
AUC_{24}, ng.hr/mL	437.5 (30)
CL/F, L/hr	45.70 (30)
C_{max}, ng/mL	208.7 (38)
$t_{1/2}$, hr	1.191 ± 0.10776
T_{max}, hr	0.500 (0.450-1.00)
V_z/F, L	74.92 (23)

Source: Table 14.4.5.1
N = Total number of participants in the treatment group in the indicated population.
N2 = Number of participants contributing to the summary statistics.
N3 = Number of participants contributing to the summary statistics for t1/2 and V_z/F.
a. Geometric mean (geometric %coefficient of variation) for all except median (range) for Tmax and arithmetic mean±standard deviation for t1/2.

Figure 2. Median plasma ritlecitinib concentration (ng/ml) - time plot (linear scale) - PK concentration analysis set (protocol B7981031)



Efficacy results

Study B7981031 was a Phase 1 PK/PD study with a 7-day intervention period. Therefore, there was no efficacy data.

Safety results

Among 15 participants in the safety analysis set, 4 AEs were experienced by 3 participants. No SAEs, severe AEs or dose reductions/temporary discontinuations due to AEs were reported. One AE of urticaria led to discontinuation of study intervention and this AE was considered as treatment related (Table 10).

Table 10. Treatment-emergent adverse events (all causality) – safety analysis set

Number (%) of Participants	Ritlecitinib 20 mg QD n (%)
Participants evaluable for adverse events	15
Number of adverse events	4
Participants with adverse events	3 (20.0)
Participants with serious adverse events	0
Participants with severe adverse events	0
Participants discontinued study drug due to adverse events[a]	1 (6.7)
Participants with dose reduced or temporary discontinuation due to adverse events	0

Includes data up to 28 days after last dose of study drug.
Except for the Number of Adverse Events participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a. Participants who have an AE record that indicates that Action Taken with Study Treatment was Drug Withdrawn.
MedDRA v26.0 coding dictionary applied.

Frequency of AEs by System Organ Class and Preferred Term

The incidence and severity of TEAEs for all participants in the safety analysis set are summaried by SOC and PT in Table 11.

Three participants experienced 4 TEAEs during the study: one experienced vomiting and nausea (both mild and not treatment-related), one experienced myalgia (mild and not treatment-related), and one experienced urticaria (moderate and treatment-related) (Table 10).

The treatment-related non-serious adverse event (NSAE) of urticaria (investigator term: acute urticaria on both legs) started on Study Day 1 and lasted for 3 days and it resulted in the permanent discontinuation from the study intervention of ritlecitinib 20 mg QD after 2 dose administrations.

Table 11. Incidence and severity of TEAEs by SOC and PT (all causality) – safety analysis set

Number of Participants Evaluable for AEs	Ritlecitinib 20 mg QD (N=15)			
Severity[a]	Mild	Mod.	Sev.	Total
Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	n (%)	n (%)	n (%)	n (%)
With Any Adverse Event	2 (13.3)	1 (6.7)	0	3 (20.0)
GASTROINTESTINAL DISORDERS	1 (6.7)	0	0	1 (6.7)
Nausea	1 (6.7)	0	0	1 (6.7)
Vomiting	1 (6.7)	0	0	1 (6.7)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (6.7)	0	0	1 (6.7)
Myalgia	1 (6.7)	0	0	1 (6.7)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (6.7)	0	1 (6.7)
Urticaria	0	1 (6.7)	0	1 (6.7)
Total preferred term events	3	1	0	4

a. If the same participant in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence is counted.
Participants are counted only once per treatment per event.
For the TESS algorithm any missing severities have been imputed as severe unless the participant experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity is summarized. Missing baseline severities are imputed as mild. Treatment (Trt) column gives study treatment at time of adverse event.
Includes data up to 28 days after last dose of study drug.
Maximum severity at any dictionary level is calculated after the report subset criteria is applied.
MedDRA v26.0 coding dictionary applied.

No deaths, adverse events of special interest (AESIs) or modifications or temporary discontinuation of the study intervention due to AEs were reported in this study.

Other Safety Evaluations

No clinically significant changes were observed in clinical laboratory and vital signs.

The most frequently reported laboratory test abnormalities were neutrophils (10^9/L) <0.8 × lower limit of normal (LLN) (4 participants), followed by lymphocytes (10^9/L) >1.2× upper limit of normal (ULN) (3 participants) and monocytes/leukocytes (%) >1.2 × ULN (3 participants) (Table 12).

One participant met the criteria of diastolic blood pressure (DBP) <50 mmHg, and 1 participant met the criteria of decrease of DBP ≥20 mmHg.

Table 12. Incidence of laboratory test abnormalities (without regard to baseline abnormality) – safety analysis set

Laboratory Abnormalities: Number of Participants Evaluable for Laboratory Abnormalities: Number (%) of Participants with Laboratory Abnormalities:			Ritlecitinib 20 mg QD 15 10 (66.7%)	
Group	**Parameter (Units)**	**Primary Criteria**	**N**	**n (%)**
HEMATOLOGY	Leukocytes (10^9/L)	< 0.6x LLN	13	1 (7.7)
	Lymphocytes (10^9/L)	> 1.2x ULN	13	3 (23.1)
	Lymphocytes/Leukocytes (%)	> 1.2x ULN	13	2 (15.4)
	Neutrophils (10^9/L)	< 0.8x LLN	13	4 (30.8)
	Neutrophils/Leukocytes (%)	< 0.8x LLN	13	1 (7.7)
	Eosinophils (10^9/L)	> 1.2x ULN	13	2 (15.4)
	Eosinophils/Leukocytes (%)	> 1.2x ULN	13	1 (7.7)
	Monocytes/Leukocytes (%)	> 1.2x ULN	13	3 (23.1)
CLINICAL CHEMISTRY	Albumin (g/dL)	> 1.2x ULN	15	1 (6.7)
	Glucose -FASTING (mg/dL)	< 0.6x LLN	15	1 (6.7)

NOTE: N = total number of participants with at least one observation of the given laboratory test while on study treatment or during lag time (28 days).
n = number of participants with a laboratory abnormality meeting specified criteria while on study treatment or during lag time (28 days).
Percentages are displayed for the laboratory tests having a category with >= 1 evaluable participants.

Taste assessment

All 15 participants were eligible for the pediatric taste questionnaire; 14 of them completed the questionnaire. The scale ranged from 1 (most favorable) to 5 (least favorable).

On Day 1 (Table 13), all 14 (93.3%) participants selected "Yes" to "take medicine as directed". Approximately half of the participants (n=7, 46.7%) scored the overall taste of medicine with a maximum of 5. Overall mouthfeel of medicine score varied from 2 – 5; most frequent score was 2 (n=5, 33.3%), which was similar to the most frequent score for the overall volume of medicine.

On Day 7 (Table 14), all 14 (93.3%) participants selected "Yes" to "take medicine as directed." Approximately half of the participants scored the overall taste of medicine with a maximum of 5. The most frequent scores for the overall mouthfeel of medicine were 2 and 4 (5 participants, 33.3%, respectively). The most frequent score for overall volume of medicine was 2 (6 participants, 40.0%).

Table 13. Descriptive summary of paediatric taste questionnaire day 1 – safety analysis set

Answer	Ritlecitinib 20 mg QD (N=15) n (%)
Take Medicine As Directed	
Yes	14 (93.3)
No	0
Overall Taste of Medicine	
1	1 (6.7)
2	0
3	3 (20.0)
4	3 (20.0)
5	7 (46.7)
Overall Mouthfeel of Medicine	
1	0
2	5 (33.3)
3	3 (20.0)
4	4 (26.7)
5	2 (13.3)
Overall Volume of Medicine	
1	2 (13.3)
2	5 (33.3)
3	2 (13.3)
4	2 (13.3)
5	3 (20.0)

Table 14. Descriptive summary of pediatric taste questionnaire day 7 – safety analysis set

Answer	Ritlecitinib 20 mg QD (N=15) n (%)
Take Medicine As Directed	
Yes	14 (93.3)
No	0
Overall Taste of Medicine	
1	0
2	1 (6.7)
3	4 (26.7)
4	2 (13.3)
5	7 (46.7)
Overall Mouthfeel of Medicine	
1	0
2	5 (33.3)
3	3 (20.0)
4	5 (33.3)
5	1 (6.7)
Overall Volume of Medicine	
1	1 (6.7)
2	6 (40.0)
3	2 (13.3)
4	1 (6.7)
5	4 (26.7)

2.3.3. Discussion on clinical aspects

Results from study B7981031 titled "*An Interventional PK, PD, Phase 1, Open-Label Study to Investigate PK and PD of Multiple-Dose Ritlecitinib in Children 6 to Less Than 12 Years of Age With Severe Alopecia Areata*" in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The aim of the study is to provide characterisation of PK in children and will be utilised to update the popPK model. Further, PD and safety results as well as palatability results were reported.

According to the PIP the doses to be investigated in the planned phase 3 study should be informed by the results of the submitted study B7981031.

The dose determination to support dosing in study B7981031 is based on the following considerations:

1. The systemic exposure data generated in B7981015 for adult and adolescent participants were utilised to derive the dose recommendations for children (6 to <12 years of age) using population PK modeling and simulation analysis.

2. The dose selected for children 6 to <12 years of age in study B7981031 is expected to provide lower exposures than the 50 mg dose in the B7981015 study in adults and adolescents.

The dose of 20 mg selected for evaluation in this PK, PD study is predicted to provide exposures in children 6 to <12 years of age approximating the exposure of a 30 mg dose in adults and adolescents. Upon CHMP's request, the MAH confirmed that the bioavailability of the 20 mg capsule in relation to the 50 mg capsule and the dissolving in water is comparable. The CHMP considers that the bridge between the 20 mg formulation and the 50 mg formulation has been sufficiently supported.

Overall, the dose of 20 mg was considered to be adequate to meet the objectives of the study to characterise the PK of ritlecitinib in children.

In addition, opening the capsule and dispersing the content in water before intake may have an impact on disintegration. Nevertheless, the MAH has demonstrated that difference in in vitro disintegration did not influence the in vivo performance. Furthermore, sprinkling the content on jam, yoghurt or apple sauce did not clinically significantly impact the exposure. The somewhat lower Cmax after administration with yoghurt is not clinically relevant, as food reduces Cmax by 32%, and Litfulo can be taken with or without food. Therefore, opening the capsule and dispersing the content in water before intake is justified.

Pharmacodynamics

Only minor, and clinically irrelevant changes in lymphocyte subsets and IP-10 levels were shown from baseline to day 7. The short duration of the intervention likely explains the absence of change in lymphocyte subsets, as described in the SmPC.

Pharmacokinetics

Plasma samples were analysed for ritlecitinib by a validated analytical method. Upon CHMP's request, the MAH confirmed that the analytical method was submitted at the time of initial MAA. In addition, accuracy and precision have been demonstrated. The issue is considered to be resolved.

During analysis of subject plasma samples results showed acceptable performance of the method. Incurred sample reanalysis indicated good reproducibility.

Following multiple oral q.d administration of 20 mg ritlecitinib capsules, plasma concentrations of ritlecitinib on day 7 had a median t_{max} of approximately 0.5 hour. Ritlecitinib mean terminal t½ was approximately 1.19 hours. Geometric mean values for ritlecitinib exposure parameters $AUC_{0\text{-}24h}$ and C_{max} were 437.5 ng.hr/ml and 208.7 ng/ml, respectively. The geometric mean CL/F was 45.70 l/h and

mean Vz/F was approximately 74.92 l. The variability (geometric %CV) for $AUC_{0\text{-}24h}$ and C_{max} was 30% and 38%, respectively.

The data will be utilised to update the population PK model which was previously developed for adults and adolescents and submitted within the initial MAA. Based on the updated population PK model, the following doses will be chosen for the efficacy and safety Phase 3 Study B7981027 in children 6 to <12 years of age with AA as agreed in the PIP

- a high dose which provides exposures equivalent to the currently authorised 50 mg ritlecitinib dose in adults and adolescents;
- a low dose which provides exposures equivalent to 30 mg ritlecitinib dose which was efficacious in the adult and adolescent Study B7981015.

Efficacy

No efficacy data were available in study B798031.

Safety

Four AEs were reported by three participants (20%), most were mild and not treatment-related (vomiting, nausea, myalgia) and one was assessed moderate and treatment-related (urticaria) which led to study discontinuation.

Two occurrences of the NSAE vomiting were experienced by a participant on Day 6 (no exact time was collected), and it was unknown whether the vomiting occurred within 1 hour after the administration of study intervention. As this could impact the PK and thus impact the outcome of the popPK modelling, the MAH was requested to clarify how the data will be handled in the popPK modelling. The MAH sufficiently justified that vomiting on day 6 will not impact the PK at day 7 due to the short elimination half-life and the fact that there is no accumulation (no pre-dose concentration).

Urticaria is a known side effect in adults treated with ritlecitinib; it was among the most frequently reported adverse reactions in the adult AA study population and is listed as 'common' in section 4.8 of the currently approved SmPC.

No SAEs, severe AEs, deaths, dose reductions or temporary discontinuation due to AEs and no AESIs were reported. No clinically significant changes were observed in laboratory parameters and vital signs.

Overall treatment was safe and well tolerated, without new safety signals. No changes to the SmPC are indicated based on the current study.

Taste assessment

The overall palatability, acceptability, and tolerability of the ritlecitinib formulation were generally acceptable.

3. CHMP's overall conclusion and recommendation

☒ Fulfilled

No regulatory action required.