12 October 2023
EMA/527931/2023
Human Medicines Division

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

Jakavi

ruxolitinib

Procedure no: EMEA/H/C/002464/P46/020

Note

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

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1. Introduction

On 25 July 2023, the MAH submitted a completed paediatric study for ruxolitinib, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

No update of the product information is proposed as part of the current procedure.

A variation to update the product information with results from this study is planned to be submitted in Q4 2023.

Steps taken for the assessment	
Description	**Date**
Start of procedure	14 Aug 2023
CHMP Rapporteur Assessment Report	14 Sep 2023
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	n/a
CHMP adoption of conclusions	12 Oct 2023

2. Scientific discussion

2.1. Information on the development program

The MAH has submitted the final clinical study report for study CINC424F12201 (REACH 4) as a stand-alone submission in accordance with Article 46 of Regulation (EC) No. 1901/2006.

Study CINC424F12201 is part of a paediatric clinical development program and is a clinical measure in the ruxolitinib paediatric investigational plan (PIP) which was approved on 1 Dec 2017 (EMEA-000901-PIP03-16) and subsequently modified on 15 May 2019 (EMEA-000901-PIP03-16-M01) and on 9 April 2021 (EMEA-000901-PIP03-16-M02).

A variation to update the product information with results from this study is planned to be submitted in Q4 2023.

2.2. Information on the pharmaceutical formulation used in the study

Jakavi is marketed as 5 mg, 10 mg, 15 mg or 20 mg tablets.

In study F12201, ruxolitinib was administered as 5 mg tablet (adult and adolescent formulation) or as an oral paediatric formulation (administered as oral solution or capsule dispersed in liquid).

Table 1. Study medication batch numbers

Study drug and strength	Batch number
Ruxolitinib 5 mg (tablet formulation)	S0046, SDD16, SLN73, STU72
Ruxolitinib 5mg/ml oral pediatric formulation	2037218, 2038806
Ruxolitinib 2.5 mg hard non-gelatin capsule formulation	1010023170, 1010024384, 1010025282
Ruxolitinib 1.5 mg hard non-gelatin capsule formulation	1010023649, 1010024382, 1010025280
Ruxolitinib 1 mg hard non-gelatin capsule formulation	1010023186, 1010024383

2.3. Clinical aspects

2.3.1. Introduction

Ruxolitinib (Jakavi/Jakafi, INC424, INCB018424 phosphate) is an oral selective inhibitor of the Janus kinases (JAKs) JAK1 and JAK2.

In the EU, Jakavi is approved for the following indications:

- Myelofibrosis (MF)
  Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.
- Polycythaemia vera (PV)
  Jakavi is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea.
- Graft versus host disease (GvHD)
  Jakavi is indicated for the treatment of patients aged 12 years and older with acute graft versus host disease or chronic graft versus host disease who have inadequate response to corticosteroids or other systemic therapies (see section 5.1).

Treatment with ruxolitinib in patients with acute GvHD was investigated in Study C2301, a Phase III randomized, open label study to investigate the efficacy and safety of ruxolitinib versus investigator-choice Best Available Therapy (BAT) added to the patient's immunosuppressive regimen in adults and adolescents ≥12 years old with Grade II-IV SR-acute GvHD. Efficacy data from the Study C2301 showed that ruxolitinib provides relevant clinical benefit for patients 12 years of age or older with acute GvHD not adequately responding to steroids or other systemic therapies. Study C2301 data, including data in adolescents, were generated in compliance with the Pediatric Investigation Plan (000901-PIP03-16-M02) and submitted as part of a type II variation to extend the indication for the treatment of acute GvHD. The indication extension was submitted in February 2021 to EMA (EMEA/H/C/002464/II/0053) and was approved by the European Commission on 29-Apr-2022.

With this procedure the MAH submitted a final report for study CINC424F12201, an open-label, single-arm, Phase I/II multi-center study conducted to investigate the PK, activity and safety of ruxolitinib added to the patient's immunosuppressive regimen in infants, children, and adolescents ages ≥28 days to <18 years old with either grade II-IV treatment naive acute GvHD or grade II-IV SR-acute GvHD.

No update of the product information is proposed as part of the current procedure.

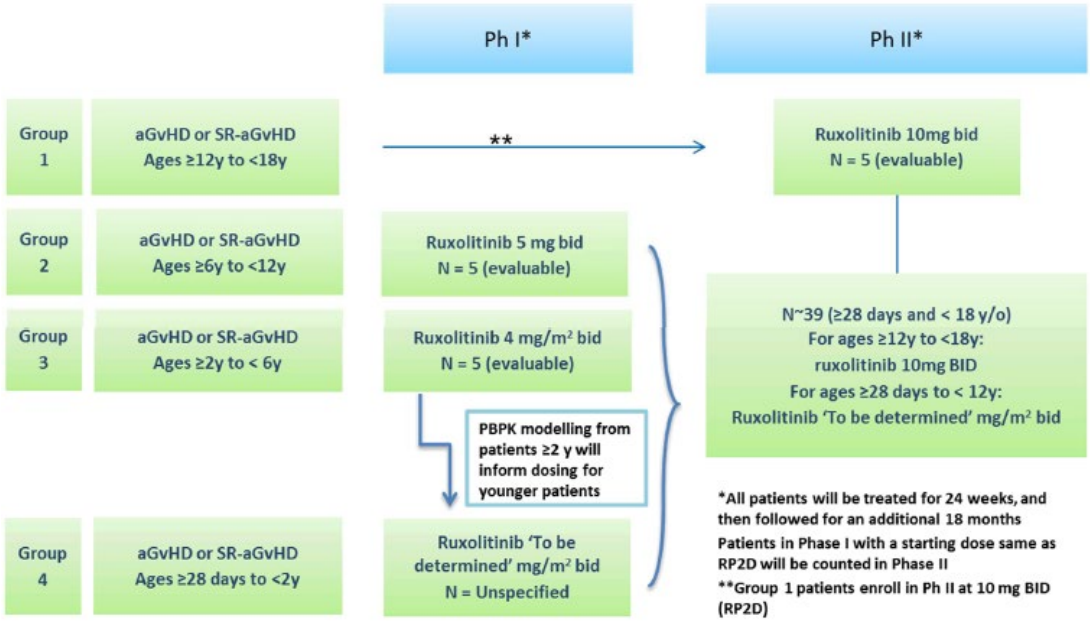
2.3.2. Clinical study CINC424F12201

Description

Study CINC424F12201 (hereafter referred to as Study F12201, also known as REACH 4) was an open-label, single-arm, Phase I/II multi-center study was conducted to investigate the PK, activity and safety of ruxolitinib added to the patient's immunosuppressive regimen in infants, children, and adolescents ages ≥28 days to <18 years old with either grade II-IV treatment naive acute GvHD or grade II-IV SR-acute GvHD.

Study design

Figure 1. Study design



The study subjects were grouped by age: Group 1 included subjects ≥12y to <18y, Group 2 included subjects ≥6y to <12y and Group 3 included subjects ≥2y to <6y. Group 4 was to include subjects ≥28 days to <2y. Subjects remained in the designated age group throughout the duration of the study, based on their age at the start of treatment.

All subjects in this study were enrolled and treated for 24 weeks (approximately 6 months) or until early discontinuation. All subjects were followed for an additional 18 months (total duration = 2 years from enrolment). Where the occurrence of acute GvHD flare required re-initiation of treatment or when extended tapering resulted in ruxolitinib not being discontinued by the end of 24 weeks, subjects could continue to taper ruxolitinib beyond 24 weeks up to a maximum of 48 weeks.

The study design consisted of Phase I and Phase II. During Phase I, PK, safety and activity data were collected for each group and used to confirm an RP2D. As subjects ≥12 y to <18 y (Group 1) had been included in Study C2301, and treated with 10 mg BID, this dose was the RP2D, and was used to treat all subjects in this age group. For Phase II, all other age groups were treated with the RP2D determined during Phase I. Therefore, all ≥12 to <18-year-old subjects were automatically enrolled in Phase II. The first 5 subjects treated in Group 1 underwent extensive PK sampling to inform the RP2D determination of the younger age groups in Phase I.

Methods

Study participants

The study population included male and female subjects ages ≥28 days to <18 years, who had undergone alloSCT, had evidence of donor-derived myeloid engraftment (ANC >1,000/µl and platelets >20,000/µl), and had been diagnosed with either treatment naïve acute GvHD grades II-IV or SR-acute GvHD grades II-IV. The final study population reflected at least 20% treatment naïve subjects and 40% SR-acute GvHD subjects.

Key inclusion criteria:

- Male or female subjects age ≥28 days and <18 years at the time of informed consent.
- Subjects who have undergone alloSCT from any donor source (matched unrelated donor, sibling, haplo-identical) using bone marrow, peripheral blood stem cells, or cord blood. Recipients of myeloablative or reduced intensity conditioning are eligible.
- Subjects with a confirmed diagnosis of grades II-IV acute GvHD within 48 hours prior to study treatment start. Subjects may have either: Treatment-naïve acute GvHD OR SR-acute GvHD as per institutional criteria, and the subject is currently receiving systemic corticosteroids.
- Evident myeloid engraftment with absolute neutrophil count (ANC) >1000/µl and platelet count >20,000/µl.

Key exclusion criteria:

- Has received the following systemic therapy for acute GvHD:
  a. Treatment-naïve acute GvHD subjects have received any prior systemic treatment of acute GvHD except for a maximum 72h of prior systemic corticosteroid therapy of methylprednisolone or equivalent after the onset of acute GvHD.
  OR
  b. SR-acute GvHD subjects have received two or more prior systemic treatment for acute GvHD in addition to corticosteroids.
- Clinical presentation resembling de novo chronic GvHD or GvHD overlap syndrome with both acute and chronic GvHD features.
- Acute GvHD occurring after non-scheduled donor leukocyte infusion (DLI) administered for pre-emptive treatment of malignancy recurrence.
- Any corticosteroid therapy for indications other than acute GvHD at doses >1 mg/kg/day methylprednisolone (or equivalent prednisone dose 1.25 mg/kg/day) within 7 days of Screening.
- Subjects who received JAK inhibitor therapy for any indication after initiation of current alloSCT conditioning.

Treatments

The study enrolled pediatric subjects who received ruxolitinib as a 5 mg tablet (adult and adolescent formulation) or as an oral pediatric formulation (administered as oral solution or capsule dispersed in liquid). All subjects received ruxolitinib twice a day for a planned duration of 24 weeks with the following starting doses:

- Group 1 (12 to 18 yr): 10 mg BID

- Group 2 (6 to 12 yr): 5 mg BID
- Group 3 (2 to 6 yr): 4 mg/m^2 BID
- Group 4 (28 days to 2 yr): to be defined by modeling.

Treatment naïve acute GvHD: in addition to ruxolitinib, treatment included methylprednisolone (or equivalent prednisone) +/- cyclosporine or tacrolimus at standard dosing adjusted to therapeutic dose levels.

SR-acute GvHD: in addition to ruxolitinib, concomitant use of corticosteroids +/- cyclosporine or tacrolimus at standard dosing adjusted to therapeutic trough levels.

In addition to study treatment, subjects received standard alloSCT supportive care including anti-infective medications and transfusion support. Continued use of systemic corticosteroids, CNI (cyclosporine or tacrolimus), and topical corticosteroid therapy per institutional guidelines was permitted. Other systemic medications used for prophylaxis of acute GvHD could be continued after Day 1 only if started prior to diagnosis of acute GvHD. For SR-acute GvHD subjects, cessation of other systemic treatment for acute GvHD other than corticosteroids +/- CNI was required prior to treatment initiation.

Objective(s) and endpoints

Primary objectives and related endpoints

Primary Objectives	Endpoints for primary objectives
• **Phase 1** To assess pharmacokinetic (PK) parameters of ruxolitinib for subjects with acute GvHD and SR-acute GvHD and define an age appropriate RP2D for each of the groups 2-4. • Group 2: age ≥ 6 to < 12 years • Group 3: age ≥ 2 to < 6 years • Group 4: age ≥ 28 days to < 2 years	• Measurement of PK parameters in acute GvHD and SR-acute GvHD subjects: AUC, Cmax, T1/2,Ctrough using extensive PK sampling in Groups 1-3 and sparse sampling in Group 4. • Age-based determination of RP2D for each of the groups 2-4, based on observed PK parameters.
• **Phase II** To measure the activity of ruxolitinib in subjects with acute GvHD or SR-acute GvHD assessed by Overall Response Rate (ORR) at Day 28.	• ORR at Day 28, defined as the proportion of subjects demonstrating a complete response (CR) or partial response (PR) without requirement for additional systemic therapies for an earlier progression, mixed response or non-response. Scoring of response will be relative to the organ stage at the start of the study treatment.

Secondary objectives and related endpoints

Secondary objectives	Endpoints for secondary objectives
• **Key secondary** To assess the rate of durable ORR at Day 56	• Proportion of all subjects who achieve a CR or PR at Day 28 and maintain a CR or PR at Day 56
• To estimate ORR at Day 14	• Proportion of subjects who achieved OR (CR+PR) at Day 14
• To assess PK/PD relationships	• PK parameters (such as AUC, Cmax, Ctrough) versus safety, efficacy, and PD biomarkers, as appropriate
• To assess Duration of Response (DOR)	• DOR is assessed for responders only and is defined as the time from first response until acute GvHD progression or the date of additional systemic therapies for acute GvHD. Onset of chronic GvHD, or death without prior observation of acute GvHD progression are considered as competing risks
• To assess the cumulative steroid dose until Day 56	• Weekly cumulative steroid dose for each subject up to Day 56
• To evaluate the safety and tolerability of ruxolitinib	• Safety and tolerability including myelosuppression, infections and bleeding will be assessed by monitoring the frequency, duration and severity of AEs including occurrence of any second primary malignancies, infections, by performing physical exams, and evaluating changes in vital signs from baseline, routine serum chemistry, hematology results and coagulation profile
• To assess Overall Survival (OS)	• OS, defined as the time from the start of treatment to the date of death due to any cause
• To assess Event-Free Survival (EFS)	• EFS, defined as the time from start of treatment to the date of hematologic disease relapse/progression, graft failure, or death due to any cause

Secondary objectives	Endpoints for secondary objectives
• To assess Failure-Free Survival (FFS)	• FFS, defined as the time from the start of treatment to date of hematologic disease relapse/progression, non-relapse mortality, or addition of new systemic acute GvHD treatment
• To assess Non-Relapse Mortality (NRM)	• NRM, defined as the time from start of treatment to date of death not preceded by hematologic disease relapse/progression
• To assess Incidence of Malignancy Relapse/Progression (MR)	• MR (refer to Appendix 16.1.1-Protocol-Section 16.3-Appendix 3), defined as the time from start of treatment to hematologic malignancy relapse/progression. Calculated for subjects with underlying hematologic malignant disease
• To measure the incidence of chronic GvHD	• Chronic GvHD, defined as the diagnosis of any chronic GvHD including mild, moderate, severe
• To estimate the rate of Best Overall Response (BOR)	• Proportion of subjects who achieved OR (CR+PR) at any time point up to and including Day 28 and before the start of additional systemic therapy for acute GvHD
• To assess graft failure	• Monitoring of donor cell chimerism, defined as initial whole blood or marrow donor chimerism > 5% declining to < 5% on subsequent measurements compared to baseline
• To describe the acceptability and palatability assessment of the ruxolitinib formulation	• Responses from the acceptability and palatability questionnaire for dose forms used after first dose, 1 month and 6 months

Outcomes/endpoints

See above.

Sample size

Phase I

Five subjects were to be enrolled to each age group with no minimum for Group 4.

A comparison of PK parameters (Cmax) from 5 evaluable pediatric subjects (in Groups 2 and 3 separately) to ~25 adult subjects (from study [Study CINC424C2301]) was performed. With expected similarity in the point estimates across groups (geo-mean ratio, GMR = 1), and accounting for expected higher variability in the pediatric subjects (CV% ~55.7%, (Loh et al 2015, detailed data on file) compared to ~40% in adults), the confidence interval for a GMR of 1 was [0.609;1.641] which demonstrates clinically relevant comparability of exposure to adult exposure (within 2-fold).

Therefore, with a minimum of 5 evaluable profiles in each of Groups 2 and 3, combined with 5 evaluable profiles from Group 1 and further sparse PK samples in the Phase II of the study, there was sufficient precision to support the PK objectives of the study. Once the RP2D was selected for Groups 2 and 3 any further eligible subjects between the ages of 2 years and 12 years were enrolled into the Phase II.

Phase II

The sample size for the Phase II objective of measuring ORR at Day 28 was 45 subjects regardless of age. Of these, at least 20% of the subjects were required to have treatment naïve acute GvHD and 40% of subjects to have SR-acute GvHD to ensure the sample was representative of the study population. The remaining enrollment could have either diagnosis. Any subject receiving the confirmed RP2D during the Phase I was counted towards the 45 subjects.

The sample size calculation for Phase II activity objective was based on the ORR at Day 28. Assuming the true ORR at Day 28 of the study population was 80%, an overall sample size of 45 subjects would have 90% probability to have a 90% CI for ORR with lower limit ≥60%. In addition, considering the Saw-Toothed behavior of power waving for single binomial proportion using an exact method, a minimum sample size of 45 subjects provided >85% probability to have a 90% CI with lower limit ≥ 60% (Chernick, Liu 2002). Subjects treated at the RP2D from the Phase I contributed to this analysis.

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

Data analysis of Phase I:

PK parameters (AUC, Cmax, Ctrough, T1/2, and other parameters, as appropriate) were derived using non-compartmental methods in subjects with extensive sampling (Groups 1, 2, and 3). These parameters, along with the safety and activity data, were then used to define the RP2D for Groups 2, 3, and 4. The observed PK parameters (within group) were summarized and compared to information obtained from adult and adolescent acute GvHD subjects treated with ruxolitinib on Study C2301. Data from subjects older than 2 years old were combined and analyzed by PBPK methods to determine the dose to be administered in subjects younger than 2 years old (Group 4).

Data analysis of Phase II:

The response rates for ORR at Day 28 were estimated with 90% CI on Efficacy Evaluable Set (EES). The confidence intervals were calculated based on the exact method for binominal distribution.

Summary statistics (frequencies and percentages) were provided. No statisical hypothesis was tested in this study.

The final analysis was conducted on all subject data at the time the trial ends. No formal interim analysis was planned for this study. Further to the regular safety monitoring conducted by the DMC and the confirmation of RP2D, activity data were analyzed when all subjects (Phase I and Phase II) completed 24 weeks (approximately 6 months) of treatment or discontinued earlier.

PK data obtained from sparse sampling were analyzed by a population PK approach along with data obtained in the Phase I part.

Results

Participant flow

A total of 45 subjects were included in this study, 18 subjects were in the ≥12y to <18y age group, 12 subjects were in the ≥6y to <12y age group, 15 subjects were in the ≥2y to <6y age group, and 0 subjects in the ≥28 days to <2y age group. Therefore, the ≥28 days to <2y age group will not be further presented in the rest of the document. All enrolled subjects received study treatment.

Table 2. Subject Disposition (All Screened Subjects)

Disposition/Reason	≥12y - <18y RUX 10mg BID N=18 n (%)	≥6y - <12y RUX 5mg BID N=12 n (%)	≥2y - <6y RUX 4mg/m² BID N=15 n (%)	All subjects N=45 n (%)
Subjects treated				
Treated	18 (100)	12 (100)	15 (100)	45 (100)
Completed treatment period	7 (38.9)	5 (41.7)	10 (66.7)	22 (48.9)
Completed and entered post treatment phase	0	3 (25.0)	3 (20.0)	6 (13.3)
Completed, did not enter post treatment	7 (38.9)	2 (16.7)	7 (46.7)	16 (35.6)
Discontinued from treatment period	11 (61.1)	7 (58.3)	5 (33.3)	23 (51.1)
Reason for treatment discontinuation				
Adverse event	5 (27.8)	3 (25.0)	2 (13.3)	10 (22.2)
Disease relapse	0	1 (8.3)	0	1 (2.2)
Lack of efficacy	6 (33.3)	3 (25.0)	3 (20.0)	12 (26.7)
Study Completion				
Completed study period	11 (61.1)	10 (83.3)	14 (93.3)	35 (77.8)
Discontinued from study period	7 (38.9)	2 (16.7)	1 (6.7)	10 (22.2)
Reason for study discontinuation				
Death	6 (33.3)	2 (16.7)	1 (6.7)	9 (20.0)
Physician decision	1 (5.6)	0	0	1 (2.2)

Of the 45 subjects enrolled, 35 subjects (77.8%) completed the study as per protocol and 10 subjects (22.2%) discontinued early from study. Of the 10 subjects who discontinued early from study, 7 subjects (38.9%) were in the ≥12y to <18y age group, 2 subjects (16.7%) were in the ≥6y to <12y age group, and 1 subject (6.7%) was in the ≥2y to <6y age group. The most common reason for early study discontinuation was 'Death' (20%, n=9), followed by 'Physician decision' (2.2%, n=1).

Of the 45 subjects who received treatment, 22 subjects (48.9%) completed the study treatment as per protocol and 23 subjects (51.1%) discontinued study treatment early. Of the 22 subjects who completed treatment, 6 subjects (13.3%) entered the post-treatment phase following early response and ruxolitinib taper. These subjects completed treatment early however continued visits as per protocol until Week 24. Of the 23 subjects who discontinued from the study treatment early, 11

subjects (61.1%) were in the ≥12y to <18y age group, 7 subjects (58.3%) were in the ≥6y to <12age group, and 5 subjects (33.3%) were in the ≥2y to <6y age group. The most common reason for early treatment discontinuation was 'Lack of efficacy' (26.7%, n=12), followed by 'Adverse event' (22.2%, n=10), and 'Disease relapse' (2.2%, n=1).

Recruitment

Study initiation date: 21-Feb-2019 (first subject first visit)

Study completion date: 02-Feb-2023 (last subject last visit)

Data cut-off date: 02-Feb-2023

Baseline data

Demographic characteristics

Of the 45 subjects, the majority were male (62.2%), white (44.4%), and not Hispanic/Latino (48.9%). The median weight (kg) was 44.5 (ranged: 36.9-85.5) in the ≥12y to <18y age group, 22.4 (ranged: 17.8-27.6) in the ≥6y to <12y age group, and 14.5 (ranged: 9.0-22.5) in the ≥2y to <6y age group. The median BMI (kg/m2) was 18.6 (ranged: 15.4-28.2) in the ≥12y to <18y age group, 16.1 (ranged: 11.9-19.1) in the ≥6y to <12y age group, and 16.7 (12.8-18.9) in the ≥2y to <6y age group. The median BSA (m2) was 1.4 (ranged: 1.2-2.0) in the ≥12y to <18y age group, 0.9 (ranged: 0.8-1.0) in the ≥6y to <12y age group, and 0.6 (ranged: 0.4-0.8) in the ≥2y to <6y age group.

Baseline disease characteristics

Overall, 27 subjects (60.0%) had an underlying malignancy. The most frequently reported diagnosis of underlying malignant disease was acute lymphoblastic leukemia (33.3% in the ≥12y to <18y age group, 58.3% in the ≥6y to <12y age group, and 13.3% in the ≥2y to <6y age group). The most frequently reported diagnosis of underlying non-malignant disease was severe aplastic anemia (11.1% in the ≥12y to <18y age group, 16.7% in the ≥6y to <12y age group, and 20.0% in the ≥2y to 6y age group).

The median time from diagnosis of underlying disease to screening was 63.9 weeks (ranged: 14.1-801.0) in the ≥12y to <18y age group, 143.6 weeks (ranged: 21.9-287.9) in the ≥6y to <12y age group, and 43.9 weeks (ranged: 23.1-130.7) in the ≥2y to <6y age group. The median time from diagnosis of underlying disease to transplant was 45.4 weeks (ranged: 10.9-796.9) in the ≥12y to <18y age group, 139.6 weeks (ranged: 17.9-282.6) in the ≥6y to <12y age group, and 37.9 weeks (ranged: 10.7-89.0) in the ≥2y to <6y age group.

Overall, based on the CIBMTR assessment, 10 subjects (22.2%) were low risk, 9 subjects (20%) were intermediate risk, and 9 subjects (20.0%) were high risk. All other subjects were either "unknown" (12 subjects; 26.7%) or "missing" (5 subjects; 11.1%).

Transplant related disease history

Overall, 34 subjects (75.6%) had myeloablative, 3 subjects (6.7%) had non-myeloablative, 7 subjects (15.6%) had reduced intensity, and 1 subject's (2.2%) conditional regimen type was missing.

Acute GvHD disease history

Of the 45 subjects enrolled, 13 subjects (28.9%) were treatment naive and 32 subjects (71.1%) had SR-acute GvHD. For 13 subjects with treatment naive, 3 subjects (16.7%) were in the ≥12y to <18y age group, 6 subjects (50.0%) were in the ≥6y to <12y age group, and 4 subjects (26.7%) were in the

≥2y to <6y age group. For the 32 subjects with SR-acute GvHD, 15 subjects (83.3%) were in the ≥12y to <18y age group, 6 subjects (50.0%) were in the ≥6y to <12y age group, and 11 subjects (73.3%) were in the ≥2y to <6y age group.

Overall, 29 subjects (64.4%) had Grade 2 acute GvHD, 12 subjects (26.7%) had Grade 3 acute GvHD, and 4 subjects (8.9%) had Grade 4 acute GvHD at baseline.

Acute GvHD organ involvement at baseline was observed in skin (34 subjects; 75.6%), lower GI (18 subjects; 40.0%), upper GI (10 subjects; 22.2%), and liver (3 subjects; 6.7%).

The mean (SD) steroid dose at start of study treatment (mg/kg/day) was 2.1 (1.10) in the ≥12y to <18y age group, 2.0 (0.69) in the ≥6y to <12y age group, and 1.8 (1.06) in the ≥2y to <6y age group.

Other relevant medical conditions

Overall, 41 subjects (91.1%) had relevant medical history or current medical conditions: 17 subjects (94.4%) in the ≥12y to <18y age group, 12 subjects (100.0%) in the ≥6y to <12y age group, and 12 subjects (80.0%) in the ≥2y to <6y age group. The most commonly reported medical history was hypertension (9 subjects; 20.0%), followed by pyrexia (8 subjects; 17.8%).

Number analysed

Table 3. Analysis sets (All screened subjects)

Analysis set	≥12y - <18y RUX 10mg BID N=18 n (%)	≥6y - <12y RUX 5mg BID N=12 n (%)	≥2y - <6y RUX 4mg/m² BID N=15 n (%)	All subjects N=45 n (%)
Full analysis set	18 (100)	12 (100)	15 (100)	45 (100)
Treatment-naive	3 (16.7)	6 (50.0)	4 (26.7)	13 (28.9)
Steroid Refractory acute GvHD	15 (83.3)	6 (50.0)	11 (73.3)	32 (71.1)
Safety set	18 (100)	12 (100)	15 (100)	45 (100)
Treatment-naive	3 (16.7)	6 (50.0)	4 (26.7)	13 (28.9)
Steroid Refractory acute GvHD	15 (83.3)	6 (50.0)	11 (73.3)	32 (71.1)
Pharmacokinetic analysis set	14 (77.8)	11 (91.7)	15 (100)	40 (88.9)
Treatment-naive	1 (5.6)	5 (41.7)	4 (26.7)	10 (22.2)
Steroid Refractory acute GvHD	13 (72.2)	6 (50.0)	11 (73.3)	30 (66.7)
Evaluable Efficacy Set	18 (100)	12 (100)	15 (100)	45 (100)
Treatment-naive	3 (16.7)	6 (50.0)	4 (26.7)	13 (28.9)
Steroid Refractory acute GvHD	15 (83.3)	6 (50.0)	11 (73.3)	32 (71.1)

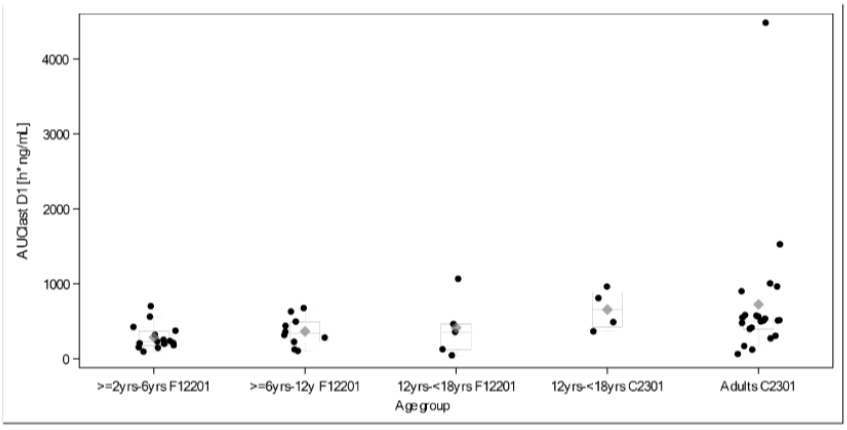
Clinical pharmacology results

The current paragraph summarizes the pharmacokinetic results from the paediatric patients in Study F12201. The results are mainly presented in terms of non-compartmental analysis (NCA)-based results and/or graphical analysis plots from patients with extensive PK sampling. The Pharmacokinetic Analysis Set from study F12201 included 45 subjects. However, only 30 patients had extensive PK sampling and were considered evaluable for calculation of NCA parameters. Patients without extensive PK sampling were subject to a sparse PK sampling design and analysed using a population PK approach (not covered in the current assessment report).

The following PK results from Study F12201 are presented per age group. However, it should be noted that patients within the lower age groups (6-12y and 2-6y) received different formulations.

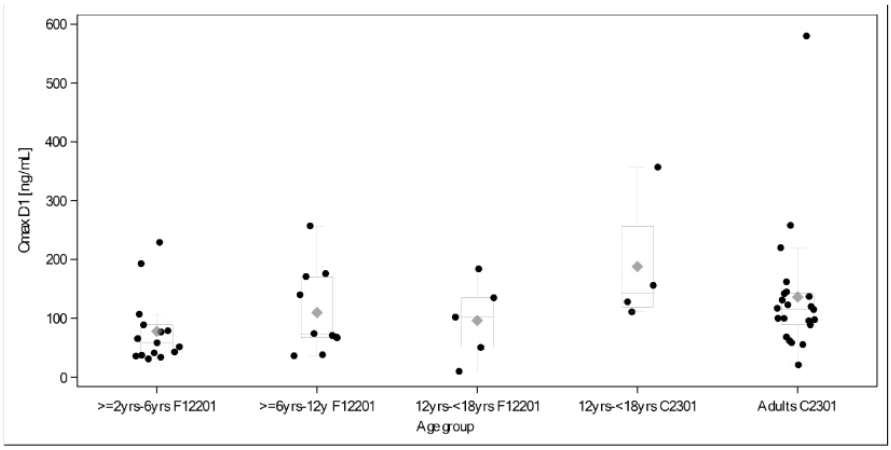
The PK parameters AUClast on Day 1, Cmax on Day 1 and Ctrough on Day 7 are shown below, including a comparison to external data from study C2301 which included adults and adolescents.

Figure 14.2-2.4 (Page 1 of 3)
Boxplot of PK Parameter for age group (F12201) and adult/adolescents (C2301)
Pharmacokinetic Analysis Set



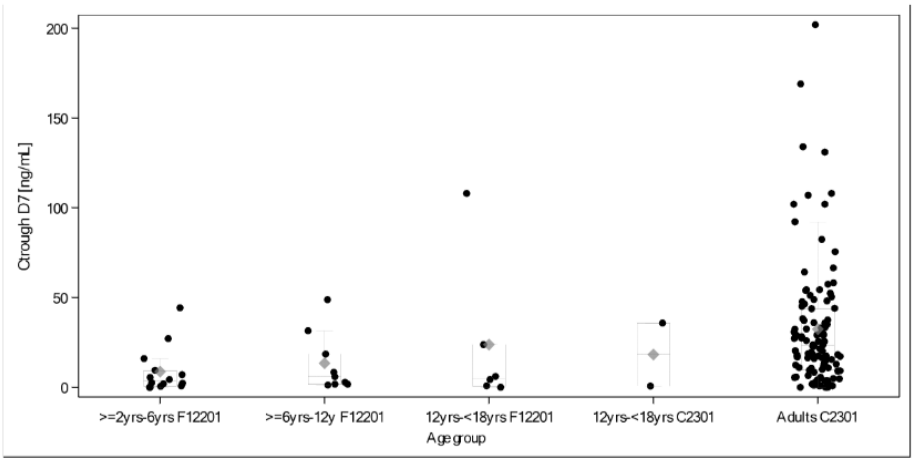
Diamond represents the mean and circle represents values outside of 1.5*IQR.
Lower and upper whiskers extend to most extreme points within 1.5*IQR of Q1 and Q3, respectively.

Figure 14.2-2.4 (Page 2 of 3)
Boxplot of PK Parameter for age group (F12201) and adult/adolescents (C2301)
Pharmacokinetic Analysis Set



Diamond represents the mean and circle represents values outside of 1.5*IQR.
Lower and upper whiskers extend to most extreme points within 1.5*IQR of Q1 and Q3, respectively.

Figure 14.2-2.4 (Page 3 of 3)
Boxplot of PK Parameter for age group (F12201) and adult/adolescents (C2301)
Pharmacokinetic Analysis Set



Diamond represents the mean and circle represents values outside of 1.5*IQR.
Lower and upper whiskers extend to most extreme points within 1.5*IQR of Q1 and Q3, respectively.

A statistical analysis was conducted, comparing the PK parameters AUClast on Day 1, Cmax on Day 1 and Ctrough on Day 7 in paediatric patients vs the corresponding PK parameters in adults+adolescents from Study C2301:

Table 14.2-4.3 (Page 1 of 1)
Statistical analysis on Adult + Adolescent (C2301) vs. current age group Pediatrics (F12201) on PK parameters
Pharmacokinetic Analysis Set

PK Parameter	Age Group	n	Adjusted Geo-Mean	Comparison	GMR	90% CI Lower CL	Upper CL
AUClast D1 (h*ng/mL)	C2301	26	510.97	C2301			
	F12201: 2-<6y	15	249.47	C2301 vs. 2-6y	2.048	1.358	3.089
	F12201: 6-<12y	10	311.40	C2301 vs. 6-12y	1.641	1.024	2.630
	F12201: 12-<18y	5	251.81	C2301 vs. 12-18y	2.029	1.093	3.768
Cmax D1 (ng/mL)	C2301	26	117.98	C2301			
	F12201: 2-<6y	15	64.01	C2301 vs. 2-6y	1.843	1.267	2.680
	F12201: 6-<12y	10	90.25	C2301 vs. 6-12y	1.307	0.851	2.009
	F12201: 12-<18y	5	66.14	C2301 vs. 12-18y	1.784	1.015	3.136
Ctrough Day 7 (ng/mL)	C2301	110	18.78	C2301			
	F12201: 2-<6y	12	4.79	C2301 vs. 2-6y	3.921	2.063	7.452
	F12201: 6-<12y	9	6.26	C2301 vs. 6-12y	2.999	1.442	6.236
	F12201: 12-<18y	5	8.85	C2301 vs. 12-18y	2.121	0.808	5.572

The PK data collected on day 1 are graphically summarized vs time in the figures below.

Figure 14.2-2.1 (Page 2 of 8)
Individual profiles of plasma concentrations of ruxolitinib and median versus time profile
Pharmacokinetic Analysis Set

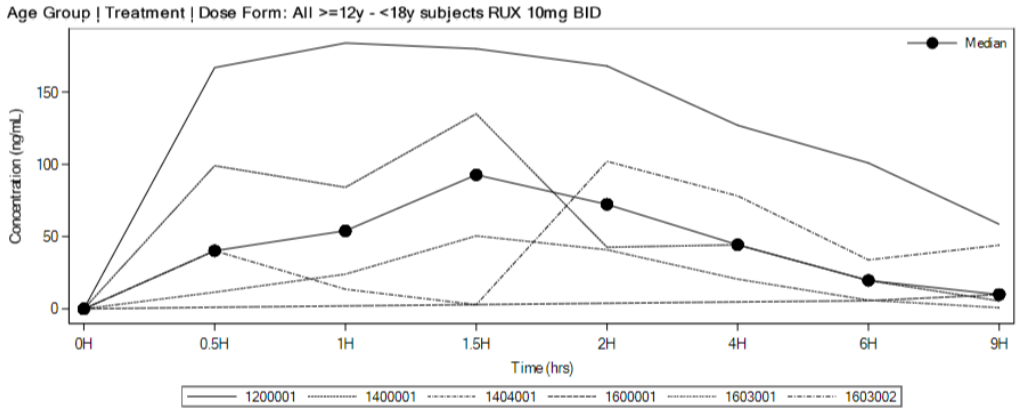


Figure 14.2-2.1 (Page 5 of 8)
Individual profiles of plasma concentrations of ruxolitinib and median versus time profile
Pharmacokinetic Analysis Set

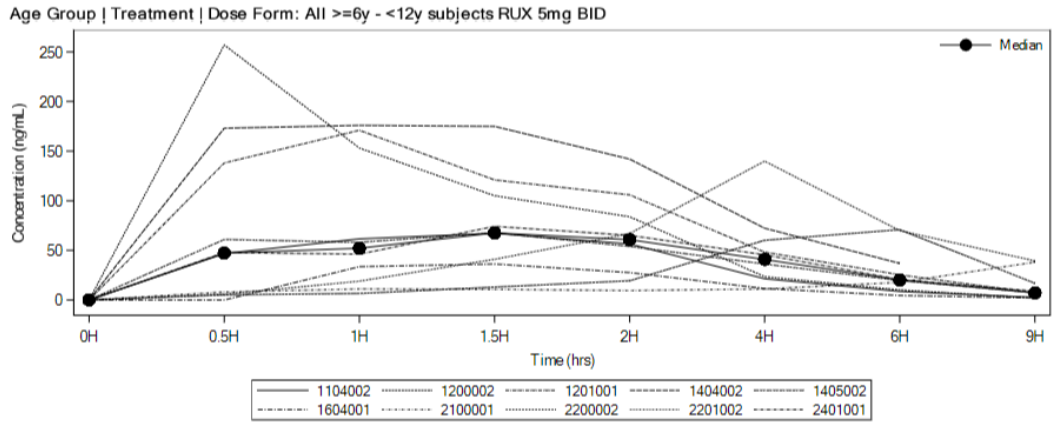
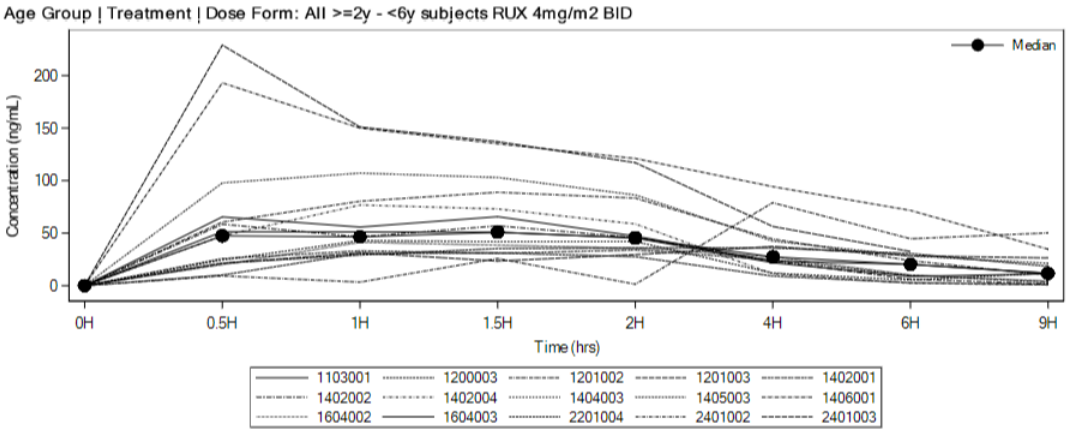


Figure 14.2-2.1 (Page 8 of 8)
Individual profiles of plasma concentrations of ruxolitinib and median versus time profile
Pharmacokinetic Analysis Set



Efficacy results

Primacy efficacy endpoint for Phase II

ORR at Day 28

Table 4. Overall Response Rate at Day 28 (Efficacy evaluable set)

	≥12y - <18y RUX 10mg BID N=18 n (%)	≥6y - <12y RUX 5mg BID N=12 n (%)	≥2y - <6y RUX 4mg/m^2 BID N=15 n (%)	All subjects N=45 n (%)
Overall response				
Responders				
Complete Response (CR)	8 (44.4)	4 (33.3)	10 (66.7)	22 (48.9)
Partial Response (PR)	7 (38.9)	6 (50.0)	3 (20.0)	16 (35.6)
Non-responders				
No response	1 (5.6)	0	1 (6.7)	2 (4.4)
Mixed response	0	0	0	0
Progression	0	0	1 (6.7)	1 (2.2)
Other *	0	0	0	0
Unknown	2 (11.1)	2 (16.7)	0	4 (8.9)
Death	0	0	0	0
Early discontinuation	2 (11.1)	2 (16.7)	0	4 (8.9)
Missing visits	0	0	0	0
Overall Response Rate (ORR: CR+PR)	15 (83.3)	10 (83.3)	13 (86.7)	38 (84.4)
90% CI for ORR	(62.3,95.3)	(56.2,97.0)	(63.7,97.6)	(72.8,92.5)

N: The total number of subjects in the treatment group. It is the denominator for percentage (%) calculation.
n: Number of subjects who are at the corresponding category.
The two sided 90% CI for the response rate was calculated using Clopper Pearson exact method.
*Other: subject with additional systemic therapies along with CR/PR per investigator assessment

ORR at Day 28 Per-protocol (sensitive analysis)

This analysis was done on 44 subjects that did not experience relevant protocol deviations.

The ORR for all subjects (N=44) was 84.1% (90% CI: 72.2, 92.3), with CR reported in 21 subjects (47.7%), and PR reported in 16 subjects (36.4%). Results of this sensitivity analysis were consistent with the primary analysis.

ORR at Day 28 by treatment-naïve vs. SR-acute GvHD (supportive analysis)

The ORR at Day 28 was 69.2% (90% CI: 42.7, 88.7) in the treatment-naïve group vs. 90.6% (90% CI: 77.5, 97.4) in the SR-acute GvHD group.

Organ response at Day 28 (supportive analysis)

Of the 34 subjects (75.6%) with baseline involvement in skin, 30 subjects (88.2%) had improvement at Day 28; of the 10 subjects (22.2%) with baseline involvement in upper GI, 7 subjects (70.0%) had improvement at Day 28; of the 18 subjects (40.0%) with baseline involvement in lower GI, 13 subjects (72.2%) had improvement at Day 28; and of the 3 subjects (6.7%) with baseline involvement in liver, 2 subjects (66.7%) had improvement at Day 28.

In general, organ responses at Day 28 in skin were comparable across all age groups.

Key secondary efficacy endpoint

Durable ORR at Day 56

Durable ORR at Day 56 was defined as the proportion of all subjects who achieved a CR or PR at Day 28 and maintained a CR or PR at Day 56.

Table 5. Durable Overall Response Rate at Day 56 (Efficacy Evaluable Set)

	≥12y - <18y RUX 10mg BID N=18 n (%)	≥6y - <12y RUX 5mg BID N=12 n (%)	≥2y - <6y RUX 4mg/m² BID N=15 n (%)	All subjects N=45 n (%)
Overall response				
Responders				
Complete Response (CR)	7 (38.9)	6 (50.0)	9 (60.0)	22 (48.9)
Partial Response (PR)	3 (16.7)	3 (25.0)	2 (13.3)	8 (17.8)
Non-responders				
No response	1 (5.6)	0	0	1 (2.2)
Mixed response	1 (5.6)	0	1 (6.7)	2 (4.4)
Progression	0	0	0	0
Other *	0	0	0	0
Unknown	3 (16.7)	1 (8.3)	1 (6.7)	5 (11.1)
Death	0	0	0	0
Early discontinuation	3 (16.7)	1 (8.3)	1 (6.7)	5 (11.1)
Missing visits	0	0	0	0
Overall Response Rate (ORR: CR+PR)	10 (55.6)	9 (75.0)	11 (73.3)	30 (66.7)
90% CI for ORR	(34.1,75.6)	(47.3,92.8)	(48.9,90.3)	(53.4,78.2)

N: The total number of subjects in the treatment group. It is the denominator for percentage (%) calculation.
N: Number of subjects who are at the corresponding category.
Durable ORR at Day 56 is defined as the proportion of all subjects who achieve a complete response (CR) or partial response (PR) at Day 28 and maintain a CR or PR at Day 56.
The two sided 90% CI for the response rate was calculated using Clopper Pearson exact method.
*Other: subject with additional systemic therapies along with CR/PR per investigator assessment

Overall, 30 subjects (66.7%) (90% CI: 53.4, 78.2) demonstrated durable ORR at Day 56, with CR reported in 22 subjects (48.9%) and PR reported in 8 subjects (17.8%). The most common reason for non-response over all was early discontinuation, reported in 5 subjects (11.1%).

- In the ≥12y to <18y age group (N=18), the durable ORR was reported in 10 subjects (55.6%) (90% CI: 34.1, 75.6), with CR reported in 7 subjects (38.9%), and PR reported in 3 subjects (16.7%).
- In the ≥6y to <12y age group (N=12), the durable ORR was reported in 9 subjects (75.0%) (90% CI: 47.3, 92.8), with CR reported 6 subjects (50.0%), and PR reported in 3 subjects (25%).
- In the ≥2y to <6y age group (N=15), the durable ORR was reported in 11 subjects (73.3%) (90% CI: 48.9, 90.3), with CR reported in 9 subjects (60.0%), and PR reported in 2 subjects (13.3%).

Other secondary efficacy endpoints

Overall response rate at Day 14

The ORR at Day 14 was 75.6% (90% CI: 62.8, 85.6), with CR reported in 16 subjects (35.6%) and PR reported in 18 subjects (40.0%).

- In the ≥12y to <18y age group (N=18), the ORR was 72.2% (90% CI: 50.2, 88.4), with CR reported in 4 subjects (22.2%), and PR reported in 9 subjects (50.0%).

- In the ≥6y to <12y age group (N=12), the ORR was 66.7% (90% CI: 39.1, 87.7), with CR reported 5 subjects (41.7%), and PR reported in 3 subjects (25.0%).
- In the ≥2y to <6y age group (N=15), the ORR was 86.7% (90% CI: 63.7, 97.6), with CR reported in 7 subjects (46.7%), and PR reported in 6 subjects (40.0%).

Duration of Response

The DOR, assessed for responders only at Day 28, was defined as the time from first response (PR or CR) until acute GvHD progression, or the date of additional systemic therapy for acute GvHD. Death without prior observation of acute GvHD progression or onset of chronic GvHD are considered to be competing risks.

From the 38 responders at Day 28, 7 subjects (18.4%) reported a loss of response, 3 subjects (7.9%) had competing risks, and 28 subjects (73.7%) were still in response at the end of the treatment period.

Median time for DOR was not reached at the time of data cut-off. The estimated probability of loss of response (progression or addition of systemic therapy for acute GvHD) at 6 months was 20.37% (95% CI: 8.74, 35.40).

Overall survival

The OS analysis was performed using follow-up data. Up to the end of study, 9 (20%) deaths were reported. None of the deaths occurred within the first 2 months from study treatment. Thirty-six subjects (80%) were alive by the end of the study.

The survival probabilities at 12 and 18 months after the start of treatment were 88.83% (95% CI: 75.22, 95.19) and 79.72 (95% CI: 64.64, 88.90), respectively.

Out of the 9 reported deaths, 6 were from the SR-acute GvHD subgroup and 3 were from the treatment-naïve group. The 12-month survival probability was 92.31% (95% CI: 56.64, 98.88) for treatment-naïve subjects and 87.39% (95% CI: 69.79, 95.07) for subjects with SR-acute GvHD.

The 18-month survival probability was 76.92% (95% CI: 44.21, 91.91) for treatment-naïve subjects and 80.92% (95% CI: 62.35, 90.95) for subjects with SR-acute GvHD.

Event-free survival

Event-free survival was defined as the time from start date of treatment to any of the following: hematologic disease relapse/progression, graft failure or death due to any cause. If a subject is not known to have any event, then EFS is censored at the latest date the subject was known to be alive (last contact date on or before the cut-off date).

No events occurred within the first month of treatment. One event occurred within the second month of treatment. The estimated probability of EFS at 6 and 12 months was 91.11 (95% CI: 78.03, 96.57), and 86.61 (95% CI: 72.59, 93.75), respectively.

Failure-Free Survival

Failure-free survival was defined as the time from start date of treatment to any of the following: hematologic relapse/progression, non-relapse mortality (NRM) or addition of new systemic acute GvHD treatment. Each type of failure is a competing risk for the other two, and onset of chronic GvHD is considered as a competing risk for all three types of failure. If it is unknown if a subject had any event or competing risk, then FFS is censored at the latest date the subject was known to be alive (last contact date on or before the cut-off date).

At the end of study, 13 subjects (28.9%) had at least one event. The number of subjects with competing risks (5 subjects, 11.1%) was lower than the number of subjects with events of interest. The estimated cumulative incidence rate of any FFS events was 13.33% (95% CI: 5.34, 25.01) at 2 months, 26.67 (95% CI: 14.72, 40.18) at 12 months, and 28.97 (95% CI: 16.48, 42.68) at 18 months and thereafter. The probability to have an additional systemic therapy at 4 months was 24%.

Non-Relapse Mortality

NRM was defined as the time from the study treatment start date to date of death not preceded by hematologic disease relapse/progression. Hematologic disease relapse/progression is considered a competing risk for NRM.

At the end of study, 6 subjects (13.3%) had an event and 3 subjects (6.7%) had competing risks. There were no events within the first 2 months from start of treatment. One subject experienced hematologic relapse/progression within first 2 months.

The estimated cumulative incidence of NRM was 8.95 (95% CI: 2.81, 19.58) at 12 months and 13.50 (95% CI: 5.40, 25.31) at 18 months and thereafter.

Incidence of Malignancy Relapse/progression

MR was defined as time from the study treatment start date to date of hematologic malignancy relapse/progression. Deaths not preceded by hematologic malignancy relapse/progression were competing risks.

There were 27 subjects who had malignant hematologic disease at baseline. Among these, 3 subjects (11.1%) had an event of MR and 4 subjects (14.8%) had competing risks at the end of study. The number of subjects censored were 20 (74.1%). Estimated cumulative incidence of MR was 7.41 (95% CI: 1.24, 21.37) at 12 months and 11.28 (95% CI: 2.74, 26.60) at 18 months and thereafter.

The rate of Best Overall Response

The BOR up to day 28 was defined as the proportion of subjects with CR or PR at any time point (up to and including Day 28 and before the start of additional systemic therapy for acute GvHD).

Overall, 42 subjects (93.3%; 90% CI: 83.7, 98.2) had either CR or PR at some time point up to Day 28, with 27 subjects (60.0%) having CR and 15 subjects (33.3%) having PR as best responses. BOR was similar between age groups. The most common reason for non-response was progression (2 subjects, 4.4%).

Cumulative steroid dosing until Day 56

The mean cumulative dose (SD) was 48.8 (30.76) mg/kg in the ≥12 to <18y age group, 65.8 (44.17) mg/kg in the ≥6 to <12 y age group, and 52.1 (21.76) mg/kg in the ≥2 to <6y age group. Overall, 17 subjects (37.8%; 95% CI: 23.8, 53.5) had completely tapered off corticosteroids and 42 subjects (93.3%; 95% CI: 81.7, 98.6) had any dose reduction by Day 56.

Overall, 43 subjects (95.6%, 95% CI: 84.9, 99.5) reported any dose reduction in steroids by EOT, with 39 subjects (86.7%, 95% CI: 73.2, 94.9) reporting a reduction greater than 50%. The median maximum dose reduction by EOT was -86.7% (range: -99.0 to -7.4). By EOT, 28 subjects (62.2%, 95% CI: 46.5, 76.2) were able to taper off steroids completely.

Incidence of chronic GvHD

Chronic GvHD was defined as the diagnosis of any chronic GvHD including mild, moderate and severe. Incidence of chronic GvHD was the time from the start of treatment to onset of chronic GvHD.

Cumulative incidence of chronic GvHD was estimated, accounting for deaths without prior onset of chronic GvHD and hematologic disease relapse/progression as the competing risks.

The cumulative incidence of chronic GvHD was 20.07 (95% CI: 9.80, 32.94) at 12 months and 24.65 (95% CI: 13.11, 38.09) at 18 months and thereafter.

Overall, 11 subjects (24.4%) developed chronic GvHD: 5 subjects (11.1%) had severe disease, 4 subjects (8.9%) had moderate disease, and 2 subjects (4.4%) had mild disease. Six subjects (13.3%) had a competing event and a total of 28 subjects (62.2%) were censored. For the 11 subjects who developed chronic GvHD the median time to onset of cGvHD was 207.0 days (ranged: 52.0-484.0).

Graft failure

At the end of the study, there were no confirmed cases of graft failure.

Acceptability and palatability

Acceptability and palatability results are presented in the CSR.

Safety results

Exposure

Overall, the median duration of exposure was 117 days ranging from 8 to 342 days. Median duration of exposure was 81 days for the ≥12y to <18y age group, 123.5 days for the ≥6y to <12y age group, and 140 days for the ≥2y to <6y age group. Overall, 26 subjects (57.8%) received ruxolitinib for at least 112 days (4 months).

Exposure by treatment-naïve and SR-acute GvHD

Median exposure was 111.0 days in treatment-naïve subjects and 127.5 days in SR-acute GvHD subjects.

Adverse events

Overall

Table 6. Overview of adverse events (Safety Set)

	≥12y - <18y RUX 10mg BID N=18		≥6y - <12y RUX 5mg BID N=12		≥2y - <6y RUX 4mg/m² BID N=15		All subjects N=45	
Category	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
Adverse events	18 (100)	16 (88.9)	12 (100)	11 (91.7)	15 (100)	12 (80.0)	45 (100)	39 (86.7)
Treatment-related	10 (55.6)	8 (44.4)	7 (58.3)	4 (33.3)	6 (40.0)	6 (40.0)	23 (51.1)	18 (40.0)
SAEs	11 (61.1)	10 (55.6)	7 (58.3)	6 (50.0)	6 (40.0)	4 (26.7)	24 (53.3)	20 (44.4)
Treatment-related	4 (22.2)	4 (22.2)	1 (8.3)	1 (8.3)	2 (13.3)	1 (6.7)	7 (15.6)	6 (13.3)
Fatal SAEs	0	0	0	0	0	0	0	0
Treatment-related	0	0	0	0	0	0	0	0
AEs leading to discontinuation	5 (27.8)	4 (22.2)	3 (25.0)	3 (25.0)	2 (13.3)	2 (13.3)	10 (22.2)	9 (20.0)
Treatment-related	4 (22.2)	3 (16.7)	2 (16.7)	2 (16.7)	2 (13.3)	2 (13.3)	8 (17.8)	7 (15.6)
AEs leading to dose adjustment/interruption	11 (61.1)	10 (55.6)	5 (41.7)	3 (25.0)	7 (46.7)	7 (46.7)	23 (51.1)	20 (44.4)
AEs requiring additional therapy	16 (88.9)	14 (77.8)	12 (100)	9 (75.0)	15 (100)	12 (80.0)	43 (95.6)	35 (77.8)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 25.1, CTCAE version 4.03.

Overall, all 45 subjects (100%) across all age groups had at least one AE, of which 39 subjects (86.7%) had an AE of ≥Grade 3. Treatment-related AEs were reported by 23 subjects (51.1%) and treatment-related AEs of ≥Grade 3 were reported by 18 subjects (40.0%). There were no fatal SAEs reported in this study. AEs leading to discontinuation were reported in 10 subjects (22.2%), of which 9 (20.0%) were ≥Grade 3.

The most commonly reported AEs by SOC were Infections and infestations (32 subjects; 71.1%), Investigations (31 subjects; 68.9%), and Blood and lymphatic system disorders (29 subjects; 64.4%). The most commonly reported AEs of ≥Grade 3 by SOC were Blood and lymphatic system disorders (27 subjects, 60.0%), followed by Investigations (23 subjects, 51.1%) and Infections and infestations (14 subjects, 31.1%).

The most commonly reported AEs by PT were anemia (20 subjects; 44.4%), neutrophil count decreased (12 subjects; 26.7%), and pyrexia (10 subjects; 22.2%). The most commonly reported AEs of ≥Grade 3 by PT were anemia (17 subjects; 37.8%), neutrophil count decreased (10 subjects; 22.2%), and neutropenia and thrombocytopenia (each reported in 9 subjects; 20.0%).

Treatment-naïve vs. SR-acute GvHD

Table 7. Overview of adverse events in treatment-naïve and SR-GvHD (Safety Set)

Category	Treatment-naive N=13		SR-acute GvHD N=32		All subjects N=45	
	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Adverse events	13 (100)	11 (84.6)	32 (100)	28 (87.5)	45 (100)	39 (86.7)
Treatment-related	5 (38.5)	3 (23.1)	18 (56.3)	15 (46.9)	23 (51.1)	18 (40.0)
SAEs	6 (46.2)	5 (38.5)	18 (56.3)	15 (46.9)	24 (53.3)	20 (44.4)
Treatment-related	2 (15.4)	2 (15.4)	5 (15.6)	4 (12.5)	7 (15.6)	6 (13.3)
Fatal SAEs	0	0	0	0	0	0
Treatment-related	0	0	0	0	0	0
AEs leading to discontinuation	3 (23.1)	2 (15.4)	7 (21.9)	7 (21.9)	10 (22.2)	9 (20.0)
Treatment-related	2 (15.4)	1 (7.7)	6 (18.8)	6 (18.8)	8 (17.8)	7 (15.6)
AEs leading to dose adjustment/interruption	5 (38.5)	3 (23.1)	18 (56.3)	17 (53.1)	23 (51.1)	20 (44.4)
AEs requiring additional therapy	11 (84.6)	8 (61.5)	32 (100)	27 (84.4)	43 (95.6)	35 (77.8)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
Treatment-related refers to relationship to investigational treatment ruxolitinib.
MedDRA version 25.1, CTCAE version 4.03.

In general, the frequency of AEs, AEs of ≥Grade 3, and AEs leading to discontinuation was similar between the two subgroups. However, treatment-related AEs and treatment-related AEs of ≥Grade 3 were reported by a higher proportion of subjects in the SR-acute GvHD group than in the treatment-naïve group.

In the treatment-naïve group, the most commonly reported SOCs were 'Infections and Infestations' and 'Investigations' each reported in 8 subjects (61.5%), followed by 'Blood and lymphatic system disorders' reported in 7 subjects (53.8%), and 'Metabolism and nutrition disorders' reported in 5 subjects (38.5%).

In the SR-acute GvHD group, the most commonly reported SOCs were 'Infections and Infestations' reported in 24 subjects (75.0%), followed by 'Investigations' reported in 23 subjects (71.9%) and 'Blood and lymphatic system disorders' reported in 22 subjects (68.8%).

Deaths

Table 8. All Deaths

Primary system organ class Primary reason (preferred term)	≥12y-<18y RUX 10mg BID N=18 n (%)	≥6y-<12y RUX 5mg BID N=12 n (%)	≥2y-<6y RUX 4mg/m² BID N=15 n (%)	All subjects N=45 n (%)
Number of subjects who died	6 (33.3)	2 (16.7)	1 (6.7)	9 (20.0)
Study indication	2 (11.1)	0	0	2 (4.4)
Other	4 (22.2)	2 (16.7)	1 (6.7)	7 (15.6)
Blood and lymphatic system disorders	1 (5.6)	0	0	1 (2.2)
Thrombotic microangiopathy	1 (5.6)	0	0	1 (2.2)
Immune system disorders	3 (16.7)	0	0	3 (6.7)
Acute graft versus host disease	2 (11.1)	0	0	2 (4.4)
Chronic graft versus host disease	1 (5.6)	0	0	1 (2.2)
Infections and infestations	2 (11.1)	0	0	2 (4.4)
Sepsis	1 (5.6)	0	0	1 (2.2)
Septic shock	1 (5.6)	0	0	1 (2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (16.7)	1 (6.7)	3 (6.7)
Acute lymphocytic leukaemia recurrent	0	1 (8.3)	0	1 (2.2)
Acute myeloid leukaemia	0	1 (8.3)	0	1 (2.2)
Juvenile chronic myelomonocytic leukaemia	0	0	1 (6.7)	1 (2.2)

Numbers (n) represent counts of subjects.
All deaths occurring on-treatment or after 30 days of the last study medication are summarized.
MedDRA version 25.1.

A total of 9 deaths occurred in the study, all of which occurred post-treatment (i.e., occurring more than 30 days after treatment discontinuation) and none of which were related to study treatment. Underlying leukemia was the most common cause of death reported in 3 subjects (6.7%). Acute GvHD was reported as cause of death in 2 subjects (4.4%), followed by chronic GvHD reported as the cause of death for 1 subject (2.2%). Two subjects died due to infections (one with sepsis and other with septic shock). In one subject, thrombotic microangiopathy was the cause of death. Overall, there were 6 deaths (33.3%) in the ≥12y to <18y age group as compared to 2 death (16.7%) in the ≥6y to <12y age group and 1 death (6.7%) in the ≥2y to <6y age group.

There were no on-treatment deaths reported in this study. No deaths were reported prior to the start of study treatment.

Serious adverse events

Overall

Across all age groups, a total of 24 subjects (53.3%) reported at least one SAE, of which 20 subjects (44.4%) had an SAE of ≥Grade 3. SAEs were reported in 11 subjects (61.1%) in the ≥12y to <18y age group, 7 subjects (58.3%) in the ≥6y to <12y age group, and 6 subjects (40.0%) in the ≥2y to <6y age group. Treatment-related SAEs were reported in 4 subjects (22.2%) in the ≥12y to <18y age group, 2 subjects (13.3%) in the ≥2y to <6y age group, and 1 subject (8.3%) in the ≥6y to <12y age group. Treatment-related SAEs of ≥Grade 3 were reported in 6 subjects (13.3%). No fatal SAEs were reported in this study.

The most frequently reported SAEs by SOC were 'Infections and infestations' (12 subjects; 26.7%) and 'Blood and lymphatic system disorder' (5 subjects; 11.1%). The most frequently reported SAEs by PT were pyrexia (4 subjects; 8.9%); and acute kidney injury, febrile neutropenia, sepsis, septic shock,

and viral hemorrhagic cystitis each reported in 2 subjects (4.4%). Of note, none of these most frequently reported SAEs by PT were related to the study drug.

Treatment-naïve vs. SR-acute GvHD

Overall, SAEs were reported in 6 subjects (46.2%) in the treatment-naïve group vs. 18 subjects (56.3%) in the SR-acute GvHD group. SAEs of ≥Grade 3 were reported in 5 subjects (38.5%) in the treatment-naïve group vs. 15 subjects (46.9%) in the SR-acute GvHD group. The frequency of treatment-related SAEs and SAEs of ≥Grade 3 were comparable between two groups.

Adverse events leading to discontinuation

Overall

AEs leading to discontinuation were reported in 10 subjects (22.2%), of which 9 subjects (20.0%) reported an event of ≥Grade 3 and one subject reported an event <Grade 3. AEs of neutrophil count decreased and platelet count decreased were each reported by 2 subjects (4.4%), and all other AEs were each reported by 1 subject.

Treatment-naïve vs. SR-acute GvHD

The frequency of AEs leading to discontinuation was similar between the two groups.

Adverse events of special interest

Overall

The most frequently reported AESIs across all age groups were 'Infections excluding Tuberculosis' (32 subjects; 71.1%), 'leukopenia' (26 subjects; 57.8%), and 'Other infection' (26 subjects; 57.8%). The most frequently reported AESIs of ≥Grade 3 across all age groups were leukopenia (25 subjects; 55.6%), anemia (17 subjects; 37.8%) and thrombocytopenia (15 subjects; 33.3%).

Treatment-naïve vs. SR-acute GvHD

The most frequently reported AESIs were infections excluding tuberculosis (61.5% vs. 75.0%), leukopenia (38.5% vs. 65.6%), other infection (53.8% vs. 59.4%) in treatment-naïve group vs. SR-acute GvHD group. The most frequently reported AESIs of ≥Grade 3 were leukopenia (38.5% vs. 62.5%), anemia (23.1% vs. 43.8%), and thrombocytopenia (15.4% vs. 40.6%) in treatment-naïve group vs. SR-acute GvHD group.

2.3.3. Discussion on clinical aspects

The MAH has submitted the final study results for study CINC424F12201 in accordance with the Article 46 of Regulation (EC) No. 1901/2006.

Study (hereafter referred to as Study F12201, also known as REACH 4) was an open-label, single-arm, Phase I/II multi-center study was conducted to investigate the PK, activity and safety of ruxolitinib added to the patient's immunosuppressive regimen in infants, children, and adolescents ages ≥28 days to <18 years old with either grade II-IV treatment naive acute GvHD or grade II-IV SR-acute GvHD.

Study F12201 enrolled 45 patients, included in 3 age groups as follows: 12-<18 years: n=18; 6-<12 years: n=12 and 2-<6 years: n=15. No patients aged less than 2 years were included in the study.

Clinical Pharmacology

The plasma PK exposure data of ruxolitinib in the subset of patients with extensive PK sampling (n=~30) was presented by the Applicant. The overall geometric mean AUClast on Day 1 was 269 ng*hr/mL, characterized by high variability with a geometric-CV 78.2%. The geometric mean AUClast on Day 1 was 252 ng*hr/mL in the ≥12y to <18y age group, 311 ng*hr/mL in the ≥6y to <12y age group, and 249 ng*hr/mL in the ≥2y to <6y age group. Statistical analysis of PK parameters comparing each age group to adolescent and adult subjects from Study C2301 was provided. The Applicant considered that the peak plasma ruxolitinib concentration, AUClast and trough concentrations in paediatric subjects were in the range of what was observed in the adult study (Study C2301).

Overall, the presentation of PK data is considered relevant within the context of this p46 procedure. However, there seems to be a clear (numerical) trend of lower exposure in paediatric patients in Study F12201 compared to Study C2301. The clinical relevance of these differences should be discussed by the Applicant in a future Type II variation.

The patients in the lower age groups (6-12y and 2-6y) were treated with different dosage forms (capsules and liquid formulations). Of note, only limited number of patients in Study F12201 were treated with capsules and liquid formulations and clinical data from additional sources would most likely need to be included in a future Type II variation in order to support these new formulations.

Apart from patients with extensive PK sampling, there are also additional patients which were subject to a sparse PK sampling design. The Applicant stated that the sparse PK data was analysed using a population PK approach which is considered acceptable.

Efficacy

ORR at Day 28 in all patients was 84.4% (90% CI: 72.8, 92.5), with complete responses reported in 22 patients (48.9%). Durable ORR at Day 56 was reported in 30 patients (66.7%).

Although assessment of data is hampered by the single arm design and the small number of patients included in the study, the results in terms of ORR is generally consistent with those in the adult and adolescent population in the aGvHD indication.

Safety

The median duration of exposure across all age groups was 117 days. All patients (100%) reported at least 1 AE; grade ≥3 AEs were reported in 39 patients (86.7%). AEs were reported most commonly in the SOCs 'Infections and infestations' (71.1%) and 'Blood and lymphatic disorders' (64.4%). The most common AEs were anaemia (44.4%), neutrophil count decreased (26.7%) and pyrexia (22.2%).

Nine patients (20.0%) died during the study with leukaemia reported as the most common cause of death (n=3; 6.7%). There were no on-treatment deaths. SAEs were reported in 24 patients (53.3%), with AEs most commonly reported in the SOCs 'Infections and infestations' (26.7%) and 'Blood and lymphatic disorders' (11.1%).

AEs leading to discontinuation were reported in 10 patients (22.2%); the most common AEs were neutrophil count decreased and platelet count decreased in 2 patients each.

The MAH concludes that the overall safety profile is consistent with the established safety profile for ruxolitinib in adult and adolescent patients with GvHD. This conclusion is in general agreed. However, in the overview submitted as part of the current procedure, the MAH has not presented or discussed data on growth and sexual maturation; this data should be presented and discussed in the upcoming variation.

The MAH intends to submit a variation application in Q4 2023 to reflect the study results in the SmPC; no changes to the product information have been proposed by the MAH as part of the current procedure.

3. Overall conclusion and recommendation

☒ **Fulfilled:**

No further action required, however, further data are expected in the context of a variation prior any conclusion on product information amendments is made.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: Jakavi Active substance: Ruxolitinib

Study title	Study number	Date of completion	Date of submission of final study report
Definitive juvenile toxicity study in rats to determine the toxicity of ruxolitinib and to investigate the reversibility of any treatment-related effects, with particular focus on bone toxicity.	Reports name: - Study No.1570143 - Study No.1570144	- 16 Sept 2016: Study No.1570143 - 10 Nov 2017: Study No.1570144	8 Feb 2019 (EMEA/H/C/002464/II/0040) (eCTD seq 0087)

Clinical studies

Product Name: Jakavi Active substance: Ruxolitinib

Study title	Study number	Date of completion	Date of submission of final study report
Open-label, randomised, active-controlled trial to evaluate pharmacokinetics, safety and efficacy of ruxolitinib compared to best available therapy (BAT) in adults and adolescents from 12 to less than 18 years of age with corticosteroid-refractory (SR) aGvHD following allogeneic HSCT (INC424C2301)	CINC424C2301	2 Sept 2021	5 Oct 2021 (PAM for Art 46)
Open-label, randomised, active-controlled trial to evaluate pharmacokinetics, safety and efficacy of ruxolitinib compared to best available therapy (BAT) in adults and adolescents from 12 to less than 18 years of age with corticosteroid-refractory (SR) cGvHD following allogeneic HSCT (INC424D2301)	CINC424D2301	12 Apr 2023	4 May 2023 (PAM for Art 46)
Phase I/II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in pediatric subjects with Grade II-IV acute graft vs. host disease after allogeneic hematopoietic stem cell transplantation (INC424F12201)	CINC424F12201	17 Jul 2023	26 Jul 2023 (PAM for Art 46)