25 April 2025
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Human Medicines Division

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

Jakavi

Ruxolitinib

Procedure no: EMA/PAM/0000250368

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of Procedure	25 February 2025	25 February 2025
☐	CHMP Rapporteur AR	31 March 2025	31 March 2025
☐	CHMP comments	14 April 2025	14 April 2025
☐	Updated CHMP Rapporteur AR	16 April 2025	N/A
☒	CHMP outcome	25 April 2025	25 April 2025

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1. Introduction

On 7 February 2025, the MAH submitted a completed paediatric study for Jakavi, in accordance with Article 46 of Regulation (EC) No. 1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure.

A short critical expert overview has also been provided.

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

2. Scientific discussion

2.1. Information on the development program

The MAH has submitted the final clinical study report for study CINC424G12201 (hereafter referred to as Study G12201, also known as REACH 5) as a stand-alone submission in accordance with Article 46 of Regulation (EC) No. 1901/2006.

Study G12201 is part of a paediatric clinical development program and is a clinical measure in the paediatric investigational plan (PIP) for ruxolitinib (EMEA-000901-PIP04-17-M02B).

A listing of all studies included in the paediatric development program is provided in the Annex.

2.2. Information on the pharmaceutical formulation used in the study

Jakavi (ruxolitinib) is marketed as 5 mg, 10 mg, 15 mg, or 20 mg tablets and an oral solution (5 mg/mL).

In study G12201, ruxolitinib was administered as 5 mg tablets or as an oral paediatric liquid formulation (5 mg/mL).

Table 1 Study medication batch numbers

Study drug and strength	Batch number
Ruxolitinib 5 mg (Tablet formulation)	SDD16, SFJH4, SLN74, STU72, SWW48
Ruxolitinib 5 mg/mL (Oral pediatric formulation)	2038806, 2040907, 2042301, 2044196, 2048929

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)

Acute GvHD

Jakavi is indicated for the treatment of adult and paediatric patients, from the age of 28 days, with acute graft versus host disease who have inadequate response to corticosteroids or other systemic therapies (see section 5.1).

Chronic GvHD

Jakavi is indicated for the treatment of adult and paediatric patients, from the age of 6 months, with chronic graft versus host disease who have inadequate response to corticosteroids or other systemic therapies (see section 5.1).

Study G12201 (REACH 5) was an open-label, single-arm, Phase II multi-centre study investigating the activity, PK and safety of ruxolitinib added to the immunosuppressive regimens of paediatric patients aged ≥28 days to <18 years old with either moderate to severe treatment-naïve GvHD or steroid refractory (SR)-chronic GvHD.

Interim data from Study G12201 were previously assessed within variation EMEA/H/C/002464/X/0070/G. The primary analysis (data cut-off date 19-Oct-2022) was submitted in support of the paediatric GvHD extension procedure which received positive CHMP opinion on 14-Nov-2024. The final analysis was performed following the last patient's last visit on 26-Aug-2024.

The interim analysis for G12201 supported the approval of Jakavi for patients aged 6 months of age and older with chronic GvHD who have inadequate response to corticosteroids or other systemic therapies in the European Union (EMEA/H/C/002464/X/0070/G). The approval of the indication was, however, primarily based on pharmacokinetic bridging.

The final results of G12201 are now available and as the study included paediatric patients, the final study report has been submitted in accordance with Article 46 of Regulation (EC) No1901/2006.

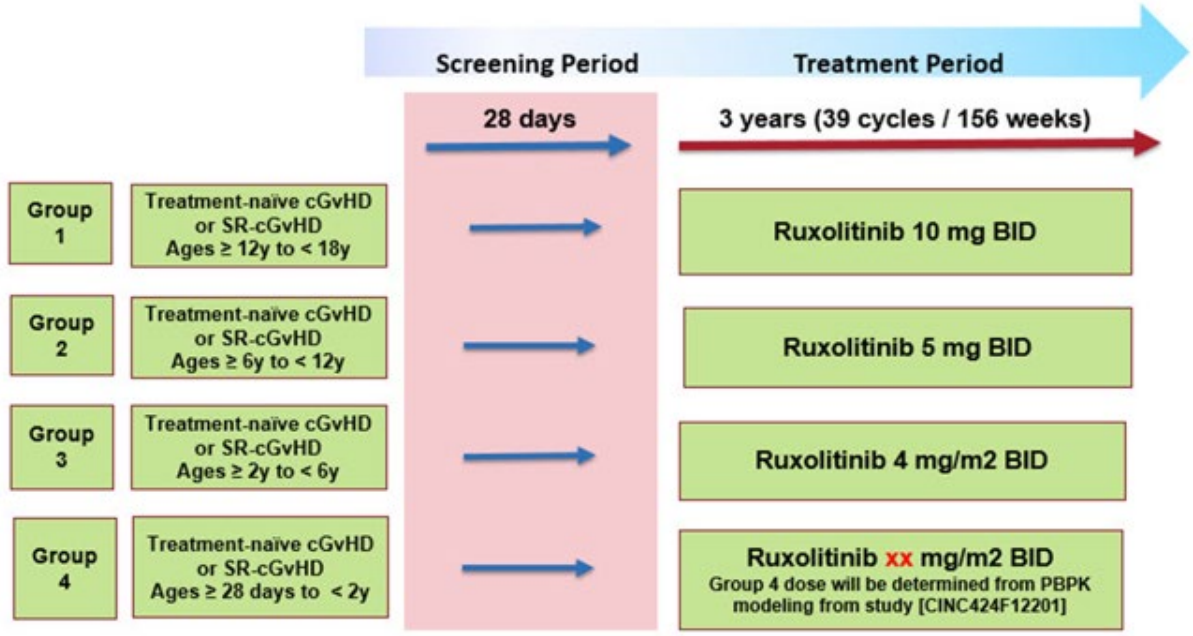
The MAH proposes no updates of the SmPC based on the final study report.

2.3.2. Clinical study CINC424G12201

Description

Study CINC424G12201 (hereafter referred to as Study G12201, also known as REACH 5) was an open-label, single-arm, Phase II multi-centre study investigating the activity, PK and safety of ruxolitinib added to the immunosuppressive regimens of paediatric patients aged ≥28 days to <18 years old with either moderate to severe treatment-naïve chronic GvHD or SR-chronic GvHD.

Figure 1 Study design



Source: [Study G12201 Figure 3-1]

Subjects were grouped according to their age:

- Group 1 included subjects ≥ 12 y to < 18 y
- Group 2 included subjects ≥ 6 y to < 12 y
- Group 3 included subjects ≥ 2 y to < 6 y
- Group 4 was to include subjects ≥ 28 days to < 2 y

After a 28-day screening period, eligible subjects started the study treatment on Cycle 1 Day 1 (C1D1) and were treated for up to a maximum of 3 years (39 cycles/156 weeks) or until early discontinuation. Subjects who discontinued study treatment for any reason earlier than 39 cycles were followed every 6 months until 3 years from their first dose of study treatment was reached.

Methods

Study participants

The study included male and female subjects ≥ 28 days to < 18 y of age, who underwent alloSCT with a donor-derived myeloid engraftment and have been diagnosed with moderate to severe treatment-naïve or SR-chronic GvHD.

Key inclusion criteria

- Male or female subjects aged ≥28 days and <18 y at the time of informed consent.
- Subjects who had undergone a successful alloSCT from any donor source (matched unrelated donor, sibling and haplo-identical) using bone marrow, peripheral blood stem cells, or cord blood. Recipients of myeloablative or reduced intensity conditioning are eligible.
- Subjects with diagnosed moderate to severe chronic GvHD according to NIH Consensus Criteria prior to C1D1, who were either:

- Treatment-naïve chronic GvHD subjects that had not received any prior systemic treatment for chronic GvHD except for a maximum 72h of prior systemic corticosteroid therapy of methylprednisolone or equivalent after the onset of chronic GvHD. Subjects were allowed to have received prior systemic treatment for chronic GvHD prophylaxis (if the prophylaxis was started prior to the diagnosis of chronic GvHD),

OR

- SR moderate to severe chronic GvHD as per institutional criteria, or per physician decision in case institutional criteria are not available, and still receiving systemic corticosteroids for the treatment of chronic GvHD for a duration of < 18 months prior to C1D1.

Key exclusion criteria

- SR-chronic GvHD subjects with a prior chronic GvHD treatment with JAK1 or a JAK2- or a JAK1/2-inhibitor are not allowed, except when the subject achieved complete or partial response and has been off JAK inhibitor treatment for at least 4 weeks prior to C1D1 or up to 5 times the half-life of the prior JAK inhibitor, whichever is longer.
- Failed prior alloSCT within the past 6 months; subjects with relapsed primary malignancy, or who have been treated for relapse after the alloSCT was performed, or who require withdrawal of immune suppression as pre-emergent treatment of early malignancy relapse.
- Subjects who initiated systemic CNI (cyclosporine or tacrolimus) within 3 weeks prior to start of ruxolitinib on C1D1. Note: Systemic CNI are allowed when initiated > 3 weeks from start of ruxolitinib.
- Any corticosteroid therapy for indications other than chronic GvHD at doses > 1 mg/kg/day methylprednisolone (or equivalent prednisone dose 1.25 mg/kg/day) within 7 days of screening visit.
- Current therapy with medications that interfere with coagulation or platelet function, including but not limited to aspirin and related drugs, heparin, and warfarin (to minimize risk of bleeding).
- Subject was receiving fluconazole at daily doses higher than 6 mg/kg (maximum 200 mg).

Treatments

Ruxolitinib was administered twice a day (BID) as a 5 mg ruxolitinib tablet or as ruxolitinib oral paediatric formulation (5 mg/mL) 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 modelling

The treatment was to be administered continuously (in cycles of 28 days) unless interruption was required to manage toxicity or for progressive disease. The planned duration of study treatment was approximately 36 months (39 cycles / 156 weeks).

For treatment-naïve chronic GvHD, in addition to ruxolitinib, treatment had to include methylprednisolone (or equivalent prednisone). For SR-chronic GvHD in addition to ruxolitinib, concomitant use of corticosteroids was required.

Objectives and endpoints

Table 2 Primary objectives and related endpoints

	Objective	**Endpoint**	**Presented in the primary or final analysis report?**
Primary	To evaluate the activity of ruxolitinib added to standard dose corticosteroids +/- CNI in paediatric subjects with moderate or severe treatment naïve- or SR chronic GvHD	ORR at C7D1 was defined as the proportion of subjects who demonstrated a CR or PR without the requirement of additional systemic therapies for an earlier progression, mixed response or non-response.	Primary analysis
Secondary	To assess PK of ruxolitinib in treatment-naïve- and SR-chronic GvHD paediatric subjects	Ruxolitinib concentrations by timepoint	Primary analysis
	To evaluate the safety of ruxolitinib	Assessed by monitoring the frequency, duration and severity of AEs that included occurrence of any second primary malignancies or infections, physical examinations, evaluation of changes in vital signs, tanner stage, changes in chemistry and hematology results from baseline.	Both
	To assess DOR	DOR was assessed for responders only. DOR was defined as the time from first response until chronic GvHD progression, death, or the date of addition of systemic therapies for chronic GvHD.	Both
	To estimate ORR at end of C3	Proportion of subjects who achieved OR (CR+PR) at C4D1	Primary analysis
	To assess BOR	Proportion of subjects who achieved OR (CR+PR) at any time point (until C7D1 or the start of additional systemic therapy for chronic GvHD)	Primary analysis + Additional analyses in Final report using data up to end of study
	To estimate the FFS	Composite time to event endpoint incorporating the following FFS events: i) relapse or recurrence of underlying disease or death due to underlying disease, ii) non-relapse mortality, or iii) addition or initiation of another systemic therapy for chronic GvHD.	Both

	To assess cumulative incidence of Malignancy Relapse (MR)	MR was defined as the time from date of treatment assignment to hematologic malignancy relapse/recurrence. Calculated for subjects with underlying hematologic malignant disease.	Both
	To assess Non-relapse mortality (NRM)	NRM was defined as the time from date of treatment assignment to date of death not preceded by underlying disease relapse/recurrence.	Both
	To assess OS	OS was defined as the time from the date of treatment assignment to the date of death due to any cause.	Both
	To assess a reduction of at least ≥ 50% in daily corticosteroid use at C7D1	Proportion of subjects with ≥ 50% reduction from baseline in daily corticosteroid dose at C7D1	Primary analysis + Additional analyses in Final report using data up to end of study
	To assess a reduction to a low dose corticosteroid dose at C7D1	Proportion of subjects with reduction from baseline in daily corticosteroid dose to ≤ 0.2 mg/kg/day methylprednisolone (or equivalent dose of ≤ 0.25 mg/kg/day prednisone or prednisolone) at C7D1	Primary analysis + Additional analyses in Final report using data up to end of study
	To assess graft failure	Graft failure was declared if the donor cell chimerism declined to < 5% on subsequent measurements. Donor cell chimerism was defined as initial whole blood or marrow donor chimerism for those who had ≥ 5% donor cell chimerism at baseline.	Both

Outcomes/endpoints

See above.

Sample size

The sample size for the primary objective of measuring ORR at C7D1 was approximately 42 subjects, regardless of age. The sample size calculation was based on the ORR at C7D1, and the calculation considered the Saw-Toothed behaviour of power waving for single binomial proportion using an exact method (Chernick and Liu 2002). Considering the response rate of children using corticosteroids is 30% to 50% (Wolff et al. 2011), it was assumed the true ORR at C7D1 of the study population was 70%, and therefore, a minimum sample size of 42 subjects would provide >80% probability to have a 90% CI with lower limit ≥ 50%.

Randomisation and blinding (masking)

N/A

Statistical Methods

The FAS was used for all baseline, demographic, and subject disposition summaries and listings, and for all efficacy analyses unless otherwise specified. The Safety Set was used for all safety analysis and summaries and listings of study treatment. PAS was used in all pharmacokinetic data analysis and PK summary statistics.

The response rates for ORR at C7D1 was estimated on the FAS as the primary endpoint. 90% CI was calculated based on the exact method for binominal distribution. Summary statistics (frequencies and percentages) were provided.

The secondary objectives in this study included the assessment of: BOR, FFS, ORR at C4D1 (end of C3), DOR, OS, NRM, MR, reduction and successful tapering of corticosteroid treatment (C7D1), PK, safety, and graft failure.

- The BOR and ORR at C4D1 were presented with their 90% CIs. The distributions for the FFS, DOR, and OS were estimated using the KM method, and the KM curves, medians, 1-, 2-, 6-, 12-, 18-, 24-, 30- and 36-month estimates with 95% CI were presented.
- Cumulative incidence of NRM and derived probabilities at Months 1, 2, 6, 12, 18, 24, 30 and 36 with 95% CI were estimated based on all subjects in the study, considering underlying disease relapse/recurrence as competing events.
- The cumulative incidence curve for MR and estimates at 1, 2, 6, 12, 18, 24, 30 and 36 months with 95% CIs were presented for subjects with underlying hematologic malignant disease, accounting for NRM as competing risk.
- The proportion of subjects with ≥ 50% reduction from baseline in daily corticosteroid dose, and the proportion of subjects with reduction from baseline in daily corticosteroid dose to methylprednisolone-equivalent steroid dose of ≤ 0.2 mg/kg/day were presented based on all subjects.
- Due to the very low number of subjects with graft failure (2 subjects), case descriptions using listings were provided.
- The assessment of safety was based primarily on the frequency of AEs, deaths, SAEs, vital signs, and clinical laboratory abnormalities. All AEs were coded with MedDRA version 27.0.
- Change from normal weight/height/BMI at baseline to abnormally low or high values while on treatment were determined through shift analysis. Abnormally low and high values were defined as below the 5th percentile and above the 95th percentile based on CDC Growth Charts, respectively.
- For PK analysis, ruxolitinib concentration sparse profiles were summarized by time point. Descriptive summary statistics were provided by age group/formulation at each scheduled time point.

An interim analysis for the efficacy and safety results was performed when all subjects completed 1 year of treatment or discontinued earlier [Study G12201 Primary analysis].

The final analysis was conducted after all subjects completed 3 years of treatment and follow-up or discontinued earlier [Study G12201 Final analysis].

Results

Participant flow

A total of 45 subjects were included and treated in this study, 22 subjects were in the ≥12y to <18y age group, 16 subjects were in the ≥6y to <12y age group, 7 subjects were in the ≥2y to <6y age group, and 0 subjects in the ≥28 days to <2y age group. No subjects were enrolled in Group 4 (≥ 28 days to < 2 y).

Table 3 Subject disposition (all screened subjects)

Disposition/Reason	≥ 12y - < 18y RUX 10mg BID N=22 n (%)	≥ 6y - < 12y RUX 5mg BID N=16 n (%)	≥ 2y - < 6y RUX 4mg/m² BID N=7 n (%)	All subjects N=45 n (%)
Subjects treated	22 (100)	16 (100)	7 (100)	45 (100)
Treatment phase ongoing	0	0	0	0
Completed treatment	3 (13.6)	5 (31.3)	3 (42.9)	11 (24.4)
Discontinued from treatment	19 (86.4)	11 (68.8)	4 (57.1)	34 (75.6)
Reason for discontinuation				
Physician decision	5 (22.7)	3 (18.8)	0	8 (17.8)
Adverse event	4 (18.2)	1 (6.3)	1 (14.3)	6 (13.3)
Lack of efficacy	4 (18.2)	1 (6.3)	1 (14.3)	6 (13.3)
Responder	3 (13.6)	2 (12.5)	0	5 (11.1)
Disease relapse	1 (4.5)	1 (6.3)	1 (14.3)	3 (6.7)
Guardian decision	1 (4.5)	1 (6.3)	1 (14.3)	3 (6.7)
Death	0	2 (12.5)	0	2 (4.4)
Graft failure	1 (4.5)	0	0	1 (2.2)
Subjects completed study	14 (63.6)	10 (62.5)	4 (57.1)	28 (62.2)
Subjects discontinued from study	8 (36.4)	6 (37.5)	3 (42.9)	17 (37.8)
Reason for discontinuation				
Death	6 (27.3)	3 (18.8)	2 (28.6)	11 (24.4)
Subject decision	0	3 (18.8)	0	3 (6.7)
Lost to follow-up	2 (9.1)	0	0	2 (4.4)

Source: Table 14.1-1.1

Of the 45 subjects who received treatment, 11 subjects (24.4%) completed the treatment as per protocol and 34 subjects (75.6%) prematurely discontinued treatment. Of the 34 subjects who prematurely discontinued treatment, 19 subjects (86.4%) were in the ≥12 y to <18 y age group, 11 subjects (68.8%) were in the ≥6 y to <12 y age group, and 4 subject (57.1%) were in the ≥2 y to <6 y age group. The most common reasons for premature discontinuation of study treatment were in descending order: 'Physician decision' (17.8%, n=8), followed by 'Adverse events' (13.3%, n=6), 'Lack of efficiency' (13.3%, n=6), and 'Responder' (11.1%, n=5).

Of the 45 subjects who received treatment, 28 subjects (62.2%) completed the study as per protocol and 17 subjects (37.8%) prematurely discontinued the study.

Of the 17 subjects (37.8%) who discontinued the study early, 8 subjects (36.4%) were in the ≥12 y to <18 y age group, 6 subjects (37.5%) were in the ≥6 y to <12 y age group, and 3 subjects (42.9%) were in the ≥2 y to <6 y age group. The reasons for premature discontinuation from the study were: 'Death' (24.4%, n=11), followed by 'Subject decision' (6.7%, n=3), and 'Lost to follow-up' (4.4%, n=2).

Recruitment

Study initiation date: 20-May-2020 (first subject first visit)

Interim analysis (data cut-off date): 19-Oct-2022 (Primary analysis)

Study completion date: 26-Aug-2024 (last subject last visit; Final analysis)

Data cut-off date: 26-Aug-2024

Baseline data

The demographic characteristics of the study population were summarised at the time of the primary analysis (for more demographic details, see the AR from Procedure no.: EMEA/H/C/002464/X/0070/G).

Demographic characteristics

Of the 45 subjects, the majority were male (N=29; 64.4%) and had SR-chronic GvHD (N=28 SR-chronic GvHD subjects). The proportions of Asian vs. Caucasian Subjects, varied in the 3 age groups (≥ 12 y to < 18 y: 63.6% vs. 36.4%; ≥ 6 y to < 12 y: 31.3% vs. 62.5%; ≥ 2 y to < 6 y: 57.1 vs. 42.9%).

Baseline-disease characteristics

The proportion of subjects with underlying malignancy was 66.7%, most frequently leukemia (60.0%).

Acute GvHD disease history

Prior acute GvHD was reported for 73.3% of subjects and was similar between the age groups. Most subjects had had grade II acute GvHD (31.1%).

Chronic GvHD disease history

At screening, the proportion of treatment-naïve subjects with severe chronic GvHD was lower (47.1%) than SR-chronic GvHD subjects with severe chronic GvHD (67.9%).

The proportion of treatment-naïve versus SR chronic GvHD in respective age group were 43.5% versus 52.2% in age group ≥ 12 y to < 18 y, 22.2% versus 66.7% in age group ≥ 6 y to < 12 y, and 42.9% versus 57.1% in age group ≥ 2 y to < 6 y.

There was a considerably higher proportion of subjects with severe chronic GvHD (62.2%) than moderate chronic GvHD (37.8%) in the overall population at screening. The ≥ 12 y to < 18 y age group had the highest proportion of subjects with severe chronic GvHD (77.3%) among the age groups. A significant proportion of subjects had lung involvement (31.1%) or liver involvement (22.2%) at screening, driven mainly by the ≥ 12 y to < 18 y age group (lung: 50.0%; liver: 27.3%).

Other relevant medical conditions

Other relevant medical conditions were summarised at the time of the primary analysis (for more details, see the AR from Procedure no.: EMEA/H/C/002464/P46/02.

Number analysed

The Full Analysis Set (FAS) comprised all subjects to whom study treatment was assigned and who received at least one dose of study treatment.

The Safety Set included all subjects who received at least one dose of study treatment. Subjects were analysed according to the study treatment received, where treatment received was defined as the assigned dose level of ruxolitinib if the subject took at least one dose of that treatment or the first dose level received if the assigned dose level was never received.

The `Listing only Set´ contained one subject who was not eligible for efficacy analyses due to protocol deviation `Patient enrolled and treated beyond local regulatory requirements´ This subject was also excluded from the safety analyses, but all safety data were provided in listings.

Table 4 Analysis sets (all screened subjects)

Analysis set	≥ 12y - <18y RUX 10mg BID N=23 n (%)	≥ 6y - <12y RUX 5mg BID N=18 n (%)	≥ 2y - <6y RUX 4mg/m² BID N=7 n (%)	All subjects N=48 n (%)
Full analysis set	22 (95.7)	16 (88.9)	7 (100)	45 (93.8)
Treatment-naive	10 (43.5)	4 (22.2)	3 (42.9)	17 (35.4)
SR cGvHD	12 (52.2)	12 (66.7)	4 (57.1)	28 (58.3)
Safety set	22 (95.7)	16 (88.9)	7 (100)	45 (93.8)
Treatment-naive	10 (43.5)	4 (22.2)	3 (42.9)	17 (35.4)
SR cGvHD	12 (52.2)	12 (66.7)	4 (57.1)	28 (58.3)
Listing only set	0	1 (5.6)	0	1 (2.1)
Treatment-naive	0	0	0	0
SR cGvHD	0	1 (5.6)	0	1 (2.1)

Percentages are computed using the number of screened subjects in each treatment group as the denominator.
Source: Table 14.1-3.1

Clinical pharmacology results

The pharmacokinetic profile in the different age groups were summarized in the primary analysis and there were no new PK data in the final analysis (for more details, see the AR from Procedure no.: EMEA/H/C/002464/X/0070/G).

Efficacy results

Primary efficacy results

The primary efficacy analysis of study G12201 was described and discussed within variation EMEA/H/C/002464/X/0070/G. The current final analysis included updated data on the secondary endpoints OS, BOR, DOR, Failure-free-survival, Malignancy relapse/recurrence, Non-relapse mortality, Reduction of daily systemic corticosteroids) and are described below.

Secondary efficacy endpoints

Overall survival

Overall, 11 subjects (24.4%) died during the study. One additional death was reported after the primary analysis [Study G12201 Final analysis-Table 11-4]. This death occurred post- treatment.

The 12-month survival rate was 84.2% (95% CI: 69.73, 92.15), and the 36-month survival rate was 74.9% (95% CI: 59.26, 85.26) [Study G12201 Final analysis-Table 11-4], [Study G12201 Final analysis-Figure 11-7].

Out of the overall 11 death cases during the study, 10 were from the SR-chronic GvHD subgroup, and 1 subject from the treatment-naïve subgroup. The 36-month survival rate was 94.1% (95% CI: 65.02, 99.15) and 63.2% (95% CI: 42.44, 78.28) for treatment-naïve and SR-chronic GvHD, respectively [Study G12201 Final analysis-Table 14.2-2.4], [Study G12201 Final analysis-Figure 11-8].

Best overall response

At the end of the study, 1 additional subject achieved PR even after 6 cycles of treatment and 8 subjects improved their response from PR to CR compared to the analysis at C7D1. Overall, 38 subjects (84.4%; 90% CI: 72.8, 92.5) had either CR or PR at some time point up to end of study, with 14 subjects (31.1%) showing CR and 24 subjects (53.3%) showing PR as best responses. The most common reason for non-response was unchanged response (5 subjects, 11.1%) [Study G12201 Final analysis-Listing 16.2.6-1.2] [Study G12201 Final analysis-Table 11-2].

Duration of response

From the 38 responders up to the end of the study, events of chronic GvHD progression, death, or starting a new systemic therapy were reported for 14 subjects (36.8%). The most common event was addition of new systemic therapy (7 subjects, 18.4%). The estimated probability to be still in response after 12 months and 18 months was 61.2% and 57.1%, respectively; and remained at 57.1% up to 36 months [Study G12201 Final analysis-Table 14.2-1.7.1].

Failure-free survival

At the end of the study, 19 subjects (42.2%) in the overall population had an event. The most frequent event was addition of new systemic therapy (24.4%), followed by death (11.1%) and underlying disease relapse/recurrence (6.7%). The 12-month FFS probability was 64.4% (95% CI: 48.67, 76.48), and the 18-month FFS probability was 57.8% (95% CI: 42.11, 70.61), which remained unchanged until 36 months. The KM median time to treatment failure was not reached [Study G12201 Final analysis-Table 11-3], [Study G12201 Final analysis-Figure 11-3].

Malignancy relapse/recurrence

By Month 2, out of 30 subjects who had underlying hematologic malignant disease, 3 subjects (10.0%) had an event of MR; by study end, no further progression events were observed. 7 subjects (23.3%) had a competing event, which included death with non-relapse mortality [Study G12201 Final analysis-Table 14.2-2.8], [Study G12201 Final analysis-Figure 11-5]. No additional events or competing risks were reported compared with the primary analysis [Study G12201 Primary analysis-Section 11.2.5].

Non-relapse mortality

At the end of the study, 9 subjects (20.0%) in the overall population, had an event of NRM; 3 subjects (6.7%) had competing events of hematologic disease relapse/progression [Study G12201 Final

analysis-Table 14.2-2.6], [Study G12201 Final analysis-Figure 11-6]. No additional event or competing risks were reported compared to primary analysis [Study G12201 Primary analysis-Section 11.2.6].

Reduction of daily systemic corticosteroids

At baseline, overall, 40 subjects (88.9%) received systemic corticosteroids, and 2 additional subjects started after C7D1 and were included in the total number of subjects. By the end of the study, 33 subjects (82.5%) had reduced corticosteroid dose by ≥ 50% from baseline at least once. Among these, 31 subjects (77.5%) received a low dose of corticosteroids (≤ 0.2 mg/kg/day), and of these, 28 subjects (70.0%) had stopped or tapered off corticosteroids completely (including due to e.g. AEs). These are 11 additional subjects compared to primary analysis, where 17 subjects (42.5%) at C7D1 had stopped or tapered off corticosteroids [Study G12201 Final analysis-Table 11-5] [Study G12201 Final analysis-Table 11-6] [Study G12201 Final analysis-Section 11.2.8] [Study G12201 Primary analysis-Table 11-9].

Graft failure

By study end, 2 subjects (4.44%) had graft failure [Study G12201 Final analysis-Listing 16.2.6-1.4].

Safety results

Exposure

Median exposure time to ruxolitinib was 12.7 months (range: 0.5 to 37.6). Median duration of exposure was highest in the ≥ 2 y to < 6 y age group (15.8 months), followed by the ≥ 6 y to <12 y age group (13.6 months), and lowest in the ≥ 12 y to < 18 y age group (9.5 months).

Exposure by treatment-naïve and SR-acute GvHD

Median exposure was longer in treatment-naïve subjects (16.0 months) than in SR-chronic GvHD subjects (11.6 months).

Adverse events

Overall

Table 5 Overview of on-treatment adverse events (Safety set)

Category	≥ 12y - < 18y RUX 10mg BID N=22		≥ 6y - < 12y RUX 5mg BID N=16		≥ 2y - < 6y RUX 4mg/m² BID N=7		All subjects N=45	
	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	22 (100)	17 (77.3)	15 (93.8)	9 (56.3)	7 (100)	5 (71.4)	44 (97.8)	31 (68.9)
Treatment-related	17 (77.3)	11 (50.0)	6 (37.5)	4 (25.0)	4 (57.1)	1 (14.3)	27 (60.0)	16 (35.6)
SAEs	15 (68.2)	12 (54.5)	7 (43.8)	5 (31.3)	4 (57.1)	4 (57.1)	26 (57.8)	21 (46.7)
Treatment-related	8 (36.4)	7 (31.8)	1 (6.3)	0	0	0	9 (20.0)	7 (15.6)
Fatal SAEs	0	0	2 (12.5)	2 (12.5)	1 (14.3)	1 (14.3)	3 (6.7)	3 (6.7)
Treatment-related	0	0	0	0	0	0	0	0
AEs leading to discontinuation	5 (22.7)	5 (22.7)	1 (6.3)	0	1 (14.3)	1 (14.3)	7 (15.6)	6 (13.3)
Treatment-related	2 (9.1)	2 (9.1)	1 (6.3)	0	0	0	3 (6.7)	2 (4.4)
AEs leading to dose adjustment/ interruption	7 (31.8)	6 (27.3)	3 (18.8)	3 (18.8)	2 (28.6)	2 (28.6)	12 (26.7)	11 (24.4)
AEs requiring additional therapy	20 (90.9)	14 (63.6)	14 (87.5)	9 (56.3)	7 (100)	4 (57.1)	41 (91.1)	27 (60.0)

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 27.0, CTCAE version 4.03.
Source: Table 14.3.1-1.1

The majority of subjects (97.8%) had at least 1 AE; 31 subjects (68.9%) had an AE of ≥ Grade 3.

Treatment-related AEs were reported by 27 subjects (60.0%) and treatment-related AEs of ≥Grade 3 were reported by 16 subjects (35.6%). Three (3) subjects (6.7%) had fatal AEs, none of which were suspected to be related to ruxolitinib. AEs leading to discontinuation of study treatment were reported in 7 subjects (15.6%), of which 6 (13.3%) were ≥Grade 3.

The most commonly reported SOCs (≥ 40.0% of all subjects) were Infections and infestations (33 subjects, 73.3%); Investigations (26 subjects, 57.8%); Blood and lymphatic system disorders (20 subjects, 44.4%); Metabolism and nutrition disorders, and Skin and subcutaneous tissue disorders (each 19 subjects, 42.2%).

The most commonly reported PTs (≥ 20% of all subjects) were anemia (11 subjects, 24.4%); COVID-19 and pyrexia (10 subjects each, 22.2%); decreased neutrophil count and upper respiratory tract infection (9 subjects each, 20.0%). The AEs with most reported ≥ grade 3 events were anemia and neutrophil count decreased (9 subjects each, 20.0%), and platelet count decreased (6 subjects, 13.3%).

Treatment-naïve vs. SR-acute GvHD

Table 6 Overview of on-treatment adverse events in treatment-naïve and SR-GvHD (Safety set)

	Treatment-naive N=17		SR-chronic GvHD N=28		All subjects N=45	
Category	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**
Adverse events	16 (94.1)	12 (70.6)	28 (100)	19 (67.9)	44 (97.8)	31 (68.9)
Treatment-related	13 (76.5)	7 (41.2)	14 (50.0)	9 (32.1)	27 (60.0)	16 (35.6)
SAEs	8 (47.1)	7 (41.2)	18 (64.3)	14 (50.0)	26 (57.8)	21 (46.7)
Treatment-related	3 (17.6)	2 (11.8)	6 (21.4)	5 (17.9)	9 (20.0)	7 (15.6)
Fatal SAEs	0	0	3 (10.7)	3 (10.7)	3 (6.7)	3 (6.7)
Treatment-related	0	0	0	0	0	0
AEs leading to discontinuation	1 (5.9)	1 (5.9)	6 (21.4)	5 (17.9)	7 (15.6)	6 (13.3)
Treatment-related	0	0	3 (10.7)	2 (7.1)	3 (6.7)	2 (4.4)
AEs leading to dose adjustment/interruption	6 (35.3)	5 (29.4)	6 (21.4)	6 (21.4)	12 (26.7)	11 (24.4)
AEs requiring additional therapy	14 (82.4)	10 (58.8)	27 (96.4)	17 (60.7)	41 (91.1)	27 (60.0)

Numbers (n) represent counts of subjects.
Treatment-related refers to relationship to investigational treatment ruxolitinib.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 27.0, CTCAE version 4.03.
Source: Table 14.3.1-7.1

In general, the frequency of AEs and grade ≥ 3 AEs was similar between the two subgroups.

Treatment-related AEs were more commonly reported in the treatment-naïve subjects (13 of 17 subjects, 76.5%) than in the SR-chronic GvHD subjects (14 of 28 subjects, 50.0%). A similar trend was observed in ≥ grade 3 related events (treatment-naïve: 7 subjects, 41.2%; SR-chronic GvHD: 9 subjects, 32.1%).

In the treatment-naïve group, the most commonly reported SOCs for treatment-related AEs were 'Investigations' reported in 5 subjects (61.5%), 'Infections and Infestations' reported in 4 subjects (23.5%), 'Blood and lymphatic system disorders' reported in 4 subjects (23.5%), and 'Metabolism and nutrition disorders' reported in 2 subjects (11.8%).

In the SR-chronic group, the most commonly reported SOCs for treatment-related AEs were 'Blood and lymphatic system disorders' reported in 9 subjects (32.1%), 'Investigations' reported in 8 subjects (28.6%), 'Infections and Infestations' reported in 4 subjects (14.3%), `Gastrointestinal disorders´ reported in 4 subjects (14.3%, 'Metabolism and nutrition disorders' reported in 2 subjects (7.1%), and `General disorders and administration site conditions' reported in 2 subjects (7.1%).

Deaths

Table 7 On-treatment deaths (Safety set)

Primary system organ class Primary reason (preferred term)	≥ 12y - < 18y RUX 10mg BID N=22 n (%)	≥ 6y - < 12y RUX 5mg BID N=16 n (%)	≥ 2y - < 6y RUX 4mg/m² BID N=7 n (%)	All subjects N=45 n (%)
Number of subjects who died	0	2 (12.5)	1 (14.3)	3 (6.7)
Study indication	0	0	0	0
Other	0	2 (12.5)	1 (14.3)	3 (6.7)
Infections and infestations	0	1 (6.3)	1 (14.3)	2 (4.4)
Aspergillus infection	0	0	1 (14.3)	1 (2.2)
Septic shock	0	1 (6.3)	0	1 (2.2)
Respiratory, thoracic and mediastinal disorders	0	1 (6.3)	0	1 (2.2)
Acute respiratory distress syndrome	0	1 (6.3)	0	1 (2.2)

Numbers (n) represent counts of subjects.
Deaths occurring during treatment or within 30 days of the last study medication are summarized.
MedDRA version 27.0.
Source: Table 14.3.1-3.1

Table 8 Post-treatment deaths (safety set)

Primary system organ class Primary reason (preferred term)	≥12y - <18y RUX 10mg BID N=22 n (%)	≥6y - <12y RUX 5mg BID N=16 n (%)	≥2y - <6y RUX 4mg/m² BID N=7 n (%)	All subjects N=45 n (%)
Number of subjects who died	6 (27.3)	1 (6.3)	1 (14.3)	8 (17.8)
Study indication	0	0	0	0
Other	6 (27.3)	1 (6.3)	1 (14.3)	8 (17.8)
Blood and lymphatic system disorders	0	1 (6.3)	0	1 (2.2)
Thrombotic microangiopathy	0	1 (6.3)	0	1 (2.2)
Cardiac disorders	1 (4.5)	0	0	1 (2.2)
Cardiac arrest	1 (4.5)	0	0	1 (2.2)
General disorders and administration site conditions	1 (4.5)	0	0	1 (2.2)
Multiple organ dysfunction syndrome	1 (4.5)	0	0	1 (2.2)
Infections and infestations	2 (9.1)	0	0	2 (4.4)
COVID-19	1 (4.5)	0	0	1 (2.2)
Pneumonia fungal	1 (4.5)	0	0	1 (2.2)
Injury, poisoning and procedural complications	1 (4.5)	0	0	1 (2.2)
Transplant failure	1 (4.5)	0	0	1 (2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (4.5)	0	1 (14.3)	2 (4.4)
Acute lymphocytic leukaemia	0	0	1 (14.3)	1 (2.2)
Leukaemia recurrent	1 (4.5)	0	0	1 (2.2)

Numbers (n) represent counts of subjects.
Deaths more than 30 days after last study medication are summarized.
MedDRA version 27.0.
Source: Table 14.3.1-3.3

A total of 11 deaths occurred during the study, one of which was related to study treatment.

There were 3 on-treatment deaths (i.e. deaths occurring up to 30 days after treatment discontinuation) all of which were due to AEs (aspergillus infection, septic shock, and acute respiratory distress syndrome), none of which were considered related to the study treatment. All 3 on-treatment deaths were from the SR-chronic GvHD subgroup.

There were 8 post-treatment deaths, all of which were due to AEs (acute and recurrent leukemia, transplant failure, infections like COVID-19 and fungal pneumonia, cardiac arrest, thrombotic microangiopathy, and multiple organ dysfunction syndrome).

One post-treatment death, due to fungal pneumonia, was suspected to be related to the study treatment. This AE started as a grade 3 SAE suspected to be related to ruxolitinib, after which ruxolitinib therapy was interrupted and then discontinued due to disease relapse; death occurred 58 days after ruxolitinib discontinuation.

Serious adverse events

Overall

SAEs were observed in 57.8% of all subjects. The SAE PTs reported in multiple subjects were pyrexia (3 subjects, 6.7%), and COVID-19, herpes zoster, hyponatremia, muscular weakness, and pneumonia (2 subjects each, 4.4%). All other SAEs were reported for 1 subject each.

There were 9 subjects (20.0%) with at least 1 SAE with suspected relationship to study treatment, of which 7 subjects (15.6%) had an SAE of grade 3 or higher. The subjects with SAEs with suspected relationship to study treatment were predominantly from the ≥ 12 y to < 18 y age group (8 out of 22 subjects, 36.4%%). One (1) of 16 subjects (6.3%) from the ≥ 6 y to < 12 y age group had a suspected study treatment-related SAE. No suspected treatment-related SAEs were reported for the ≥ 2 y to < 6 y age group.

The most commonly reported SOCs for treatment-related SAEs were Infections and infestations (3 subjects, 6.7%), and Metabolism and nutrition disorders (2 subjects, 4.4%). The only PT reported in multiple subjects was hyponatremia (2 subjects, 4.4%); all other PTs were reported for 1 subject only.

Treatment-naïve vs. SR-acute GvHD

There was a smaller proportion of subjects experiencing an SAE in the treatment naïve subgroup compared with the SR-chronic subgroup (47.1% versus 64.3%). Also, the proportion of subjects with SAEs ≥ grade 3 was smaller in the treatment naïve subgroup compared with the SR-chronic subgroup (41.2% versus 50.0%).

The frequency of SAEs suspected to be related to the study treatment was comparable for both subgroups: 17.6% versus 21.4% in the treatment naïve and SR-chronic subgroup, respectively. The frequency of grade ≥ 3 SAEs suspected to be related to the study treatment was lower in the treatment naïve subgroup compared with the SR-chronic GvHD subgroup (11.8% versus 17.9%).

Adverse events leading to discontinuation

Overall

All PTs for AEs that led to discontinuation of study treatment were reported for 1 subject each (7 subjects, 15.6% in total). All AEs leading to discontinuations were SAEs (alveolar proteinosis, aspergillus infection, herpes zoster, COVID-19, retinal vein occlusion, transplant failure), except for thrombocytopenia. Aspergillus infection and COVID-19 were later fatal. Three AEs suspected to be related to ruxolitinib which led to discontinuation of study treatment were alveolar proteinosis, thrombocytopenia, and retinal vein occlusion.

Adverse events leading to dose adjustment and/or interruption

Overall, 12 subjects (26.7%) required dose adjustment and/or interruption due to AEs, and of these, 11 subjects (24.4%) had AEs of ≥ grade 3. Most AEs leading to interruption and/or dose adjustment were reported for 1 subject each. AEs leading to dose adjustments and/or interruptions that were each reported in multiple subjects were neutrophil count decreased (3 subjects, 6.7%), and neutropenia, thrombocytopenia, ALT increased, platelet count decreased, and WBC count decreased (2 subjects each, 4.4%) [Study G12201 Final analysis-Table 14.3.1-4.8].

There were 5 SAEs that required dose adjustment (pain in extremity) or interruption (blood creatinine increased, pneumonia fungal, pneumonia respiratory syncytial viral, and septic shock). Septic shock was later fatal. Of these SAEs, pneumonia fungal, pain in extremity, and blood creatinine increased were considered related to ruxolitinib [Study G12201 Final analysis -Listing 14.3.2-1.6].

Adverse events of special interest

Overall

Overall, the most common reported AESIs were infections excluding tuberculosis, which were reported in 34 subjects (75.6%). The frequency of infections was higher in the ≥ 2 y to < 6 y (85.7%) and ≥ 6 y to < 12 y (81.3%) age groups than in the ≥ 12 y to < 18 y age group (68.2%). However, it was expected to observe a higher incidence of infections in younger subject. There were no reported AEs that fell under the AESI categories of Bruising, Dizziness, Growth retardation, Hepatitis B reactivation, Intracranial hemorrhage, Second primary malignancies, Non-melanoma skin cancers, Other cytopenias, Progressive multifocal leukoencephalopathy, or Tuberculosis.

Treatment-naïve vs. SR-acute GvHD

Treatment-naïve subjects were > 10% more likely to report viral infections, elevated transaminases, lipid abnormalities, and bacterial infections, whereas SR-chronic GvHD subjects were > 10% more likely to report infections with pathogen unspecified, erythropenia (anemia), and hypertension. Similarly, treatment-naïve subjects were > 10% more likely to report ≥ grade 3 viral infections, elevated transaminases, and lipid abnormalities, whereas SR-chronic GvHD subjects were > 10% more likely to report ≥ grade 3 infections with pathogen unspecified and erythropenia (anemia). For other categories of AESI, there was < 10% difference between treatment-naïve and SR-chronic GvHD subjects.

Development (Growth and sexual maturation)

Growth

At baseline, 29 of the 45 subjects (64.4%) had a normal BMI, and 65.5% of them remained normal post-baseline. A smaller proportion of subjects changed from normal BMI at baseline to low (10.3%) compared with high (24.1%) values post-baseline. Most subjects with abnormally low or high BMI during baseline remained with abnormally low (92.9%) or high (100%) BMI during the study; 1 subject with low baseline BMI reported at least 1 normal post-baseline value [Study G12201 Final

analysis-Figure 14.3-2.5] and [Study G12201 Final analysis-Figure 14.3-2.6], [Study G12201 Final analysis-Table 14.3-4.2].

Tanner stage

There were 2 female subjects with delayed puberty (failure to reach Tanner stage 2 breast development by age 13), and none with precocious puberty. There was 1 male subject with precocious puberty (attained Tanner stage 2 by the age of 4 years old) and 2 male subjects with delayed puberty (subject had not attained Tanner stage 2 by age 14 and 19, respectively). The remaining subjects for both sexes displayed advancing Tanner stages with increasing age. Note that all subjects with delayed puberty already had delayed puberty at study entry. [Study G12201 Final analysis-Figure 14.3-2.7] and [Study G12201 Final analysis-Figure 14.3-2.8].

2.3.3. Discussion on clinical aspects

The MAH has submitted the final study results for study CINC42G12201 (study G12201; REACH 5) in accordance with the Article 46 of Regulation (EC) No. 1901/2006.

Study G12201 was an open-label, single-arm, Phase II multi-centre study investigating the activity, PK and safety of ruxolitinib added to the immunosuppressive regimens of paediatric patients aged ≥28 days to <18 years old with either moderate to severe treatment-naïve GvHD or SR-chronic GvHD.

A total of 45 subjects were included and treated in this study, 22 subjects in the ≥12y to <18y age group, 16 subjects in the ≥6y to <12y age group, 7 subjects in the ≥2y to <6y age group, and 0 subjects in the ≥28 days to <2y age group. No subjects were enrolled to the ≥28 days to <2 y age group.

The demographic characteristics were largely balanced between the age groups, except for the proportion of SR-chronic GvHD subjects, which was higher in the ≥6 y to <12 y age group (75.0%) compared with the ≥12 y to <18 y (54.5%) and ≥2 y to <6 y (57.1%) age groups.

Efficacy

The updated data on OS, BOR and DOR etc in the final analysis of study G12201 are in line with data in the primary analysis, and do not alter the conclusions drawn within variation EMEA/H/C/002464/X/0070/G.

Safety

The median duration of exposure across all age groups was 12.7 months. Median exposure was longer in treatment naïve subjects (16.0 months) than in SR-chronic GvHD subjects (11.6 months).

The majority of subjects (97.8%) had at least 1 AE; 31 subjects (68.9%) had an AE of ≥ Grade 3. Subjects in the ≥ 12 y to < 18 y age group were more likely to have grade ≥ 3 AEs than either the ≥ 6 y to < 12 y or ≥ 2 y to < 6 y age groups (77.3% versus 56.3% versus 71.4%); however, this could be because the ≥ 12 y to < 18 y age group had a higher proportion of subjects with severe chronic GvHD at baseline compared to the other age groups.

The most commonly reported SOCs (≥ 40.0% of all subjects) were Infections and infestations (33 subjects, 73.3%); Investigations (26 subjects, 57.8%); Blood and lymphatic system disorders (20 subjects, 44.4%); Metabolism and nutrition disorders, and Skin and subcutaneous tissue disorders (19 subjects each, 42.2%).

Treatment-related AEs were more commonly reported in treatment-naïve subjects than in SR-chronic GvHD subjects (76.5% versus 50.0%). A similar trend was observed in ≥ grade 3 related events (41.2% versus 32.1%).

There were 3 on-treatment deaths, due to acute respiratory distress syndrome, aspergillus infection, and septic shock. None of these were suspected to be related to ruxolitinib. Additionally, 8 post-treatment deaths were reported. All were due to AEs (thrombotic microangiopathy, cardiac arrest, multiple organ dysfunction syndrome, COVID-19, pneumonia fungal, transplant failure, acute lymphocytic leukaemia, and leukaemia recurrent). One of the post-treatment deaths was suspected to be related to ruxolitinib. The event started as a grade 3 SAE of pneumonia fungal suspected to be related to ruxolitinib, which led to treatment discontinuation; 58 days after ruxolitinib was discontinued, the subject died due to the event.

SR-chronic GvHD subjects were more likely to have SAEs, fatal AEs, AEs leading to ruxolitinib discontinuation, or AEs requiring additional therapy than treatment-naïve subjects. This could indicate that such AEs are less likely for subjects who do not receive heavy pre-treatment prior to ruxolitinib therapy. However, the study was not powered to compare a treatment-naïve chronic GvHD population to a SR-chronic GvHD population, and care should be taken in interpreting this observation. The most commonly reported AESI group was infections excluding tuberculosis.

AEs leading to discontinuation of study drug were reported in 7 subjects (15.6%) and the PTs were alveolar proteinosis, aspergillus infection, herpes zoster, COVID-19, retinal vein occlusion, transplant failure, and thrombocytopenia.

Benefit /risk assessment

The final efficacy analysis was in line with data in the primary analysis, which is described in the SmPC. No unexpected toxicities were observed for ruxolitinib therapy, and no additional risk was identified for treatment-naïve subjects as compared to SR-chronic GvHD subjects

There were no notable findings in growth development or Tanner staging, although long-term data is limited.

Overall, the benefit/risk ratio for ruxolitinib therapy in paediatric subjects with chronic GvHD who have inadequate response to corticosteroids or other systemic therapies remains unchanged.

No changes to the product information have been proposed by the MAH as part of the current procedure, which is agreed.

3. Rapporteur's overall conclusion and recommendation

☒ **Fulfilled:**

No further action required.

4. Request for supplementary information

N/A