14 November 2024
EMA/553041/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Jakavi

International non-proprietary name: Ruxolitinib

Procedure No. EMEA/H/C/002464/X/0070/G

Note

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

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Administrative information

Name of the medicinal product:	Jakavi
MAH:	Novartis Europharm Limited Vista Building Elm Park Merrion Road Dublin 4 IRELAND
Active substance:	Ruxolitinib phosphate
International Non-proprietary Name/Common Name:	Ruxolitinib
Pharmaco-therapeutic group (ATC Code):	protein kinase inhibitors, janus-associated kinase (jak) inhibitors
Therapeutic indications:	<u>Myelofibrosis (MF)</u> 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. <u>Polycythaemia vera (PV)</u> Jakavi is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea. <u>Graft versus host disease (GvHD)</u> Acute GvHD Jakavi is indicated for the treatment of adults and paediatric patients aged 28 days and older 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 adults and paediatric patients aged 6 months and older with chronic graft versus host disease who have inadequate response to corticosteroids or other systemic therapies (see section 5.1).
Pharmaceutical form(s):	Oral solution; Tablet
Strength(s):	5 mg/ml, 5 mg, 10 mg, 15 mg and 20 mg

Route(s) of administration:	Oral use
Packaging:	blister (PVC/PCTFE/alu) and bottle (glass)
Package size(s):	14 tablets, 56 tablets, 168 (3 x 56) tablets (multipack), and 1 bottle

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List of abbreviations

aGvHD	Acute graft versus host disease
alloHSCT	Allogeneic hematopoietic stem cell transplantation
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
BAT	Best available therapy
BCS	Biopharmaceutics classification system
b.i.d.	bis in diem/twice a day
BMI	Body mass index
BMT	Bone Marrow Transplantation
BOR	Best overall response
cGvHD	Chronic graft versus host disease
CHMP	Committee for Medicinal Products for Human use
CIBMTR	Center for International Blood and Marrow Transplant Research
CML	Chronic myeloid leukemia
CMV	Cytomegalovirus
CNI	Calcineurin Inhibitor
CR	Complete response
DOR	Duration of response
EFS	Event-free survival
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
EQ-5D	Classification of five dimensions of health: mobility, self-care, usual activities, anxiety/depression, and pain/discomfort
EQ-5D-5L	Similar as EQ-5D, with new five-level severity for each dimension of health
FACT	Functional Assessment of Cancer Therapy
FAS	Full analysis set
FFS	Failure free survival
GvHD	Graft versus host disease
HNC	Hard non-gelatin capsule
HPLC	High performance liquid chromatography
HU	Hydroxyurea
IRT	Interactive response technology
JAK	Janus kinase
K-M	Kaplan-Meier
LPLV	Last patient last visit
MDS	Myelodysplastic syndromes
MF	Myelofibrosis
MR	Malignancy Relapse/Progression
NE	Not estimable
NIH	(the US) National Institute of Health
NRM	Non-relapse mortality
ORR	Overall response rate
OS	Overall survival
PBSC	Peripheral blood stem cell
PBPK	Physiologically-based pharmacokinetic
PBT	Persistent, bioaccumulative and toxic

PET-MF	Post-essential thrombocythemia myelofibrosis
PIP	Paediatric investigation plan
PK	Pharmacokinetics
PMF	Primary myelofibrosis
PPS	Per-Protocol Set
PPV-MF	Post-polycythemia vera myelofibrosis
PR	Partial response
Ph. Eur.	European Pharmacopoeia
RH	Relative humidity
ROW	Rest of world
RP2D	Recommended Phase II dose
RUX	Ruxolitinib
PV	Polycythemia vera
SR-aGvHD	Corticosteroid refractory acute Graft versus Host Disease
SR-cGvHD	Corticosteroid refractory chronic Graft versus Host Disease
STAT	Signal transducers and activators of transcription
TRM	Transplant-related mortality
TYK2	Tyrosine kinase 2
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

Novartis Europharm Limited submitted on 23 November 2023 a group of variations consisting of an extension of the marketing authorisation and the following variation:

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to introduce a new pharmaceutical form associated with a new strength (5 mg/ml oral solution) and a new route of administration (gastric use), indicated for the treatment of Graft versus host disease (GvHD) in patients aged 28 days or older.

The above line extension is grouped with a type II variation:
- C.I.6.a - To include "treatment of paediatric patients aged 28 days to less than 18 years old in acute and chronic Graft versus Host Disease" for JAKAVI, based on final results from studies REACH4 (CINC424F12201) and REACH5 (Study CINC424G12201). REACH4 is a Phase I/II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in paediatric patients with grade II-IV acute Graft vs. Host disease after allogeneic hematopoietic stem cell transplantation; while REACH5 is a Phase II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in paediatric subjects with moderate and severe chronic Graft vs. Host disease after allogeneic stem cell transplantation (both for oral solution and already approved tablets presentations). As a consequence, sections 4.1,4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

The RMP (version 16) is updated in accordance. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to implement editorial changes to Annex II.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0527/2021 (treatment of chronic graft versus host disease) and P/0172/2021 (treatment of acute graft versus host disease) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIPs P/0527/2021 (treatment of chronic graft versus host disease) and P/0172/2021 (treatment of acute graft versus host disease) were completed. The PDCO issued an opinion on compliance for both PIPs, P/0527/2021 and P/0172/2021. These two PIPs for acute and chronic GvHD (P/0527/2021 and P/0172/2021) are linked and combined together become the PIP eligible for the reward.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The MAH did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: N/A

CHMP Peer reviewer(s): N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Ulla Wändel Liminga

The application was received by the EMA on	23 November 2023
The procedure started on	28 December 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 March 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 March 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 April 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	12 August 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	18 September 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 March 2024

The CHMP agreed on a list of outstanding issues to be sent to the MAH on	17 October 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues on	21 October 2024
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	29 October 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Jakavi on	14 November 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is a well-established procedure for the treatment of malignant and non-malignant hematological diseases. However, despite the curative potential of alloHSCT, graft versus host disease (GvHD) remains a major cause of morbidity and transplant-related mortality (TRM) following alloHSCT in children.

GvHD is an immunologically mediated, multi-organ disorder that occurs when donor-derived immune cells recognize the transplant recipient cells, organs and tissues as non-self, thereby initiating an adverse immune reaction leading to tissue damage, organ failure, or even death.

Paediatric alloHSCT differs mainly in terms of heterogeneity of non-malignant diseases leading to transplantation compared to adults, and paediatric GvHD develops with a lower overall incidence than in adults. Pathophysiology and disease manifestations are, in general, similar between paediatric and adult GvHD patients (Lawitschka et al 2020, Sobkowiak-Sobierajska et al 2022, Haroun et al 2023).

In the literature, it is suggested that a better residual thymic functions in paediatric patients could contribute to the overall lower GvHD incidence in children, since the thymus may prevent the expansion of alloreactive T-cell clones (Klein et al 2001, Hauron et al 2023).

GvHD is categorized into two main clinical forms, namely acute GvHD (aGvHD) and chronic GvHD (cGvHD), although patients may also have disease characteristics of both.

2.1.2. Epidemiology and risk factors

2.1.2.1. Acute GvHD

In paediatric patients receiving alloHSCT from an unrelated donor, the incidence of grade II-IV acute GVHD ranges from 40 to 85% of recipients, depending on the degree of donor and stem cell mismatch, while the incidence is approximately 27% after alloHSCT from an HLA-identical sibling (Gatza et al 2020).

The occurrence and severity of aGvHD depends on various factors including donor type (i.e., matched or unmatched, related or unrelated), older patient/donor age, gender disparity, multiparous female donors, intensity of transplant conditioning regimen, and absence of or suboptimal GvHD prophylaxis.

Acute GvHD is one of the most consistently reported risk factors for development of cGvHD. It is estimated that approximately 30-50% of the patients with aGvHD will develop cGvHD despite the treatment received.

2.1.2.2. Chronic GvHD

The incidence of paediatric chronic GvHD shows high variability, ranging from 6 to 65%, with some differences explained by the specific transplantation indication (malignant vs. non-malignant), heterogeneity of procedures, and age-related immune reconstitution post transplantation. In general, paediatric cGvHD tends to be less common with milder symptoms than in adults. Approximately 85% of paediatric cGvHD patients have been reported to have moderate to severe cGvHD based on the NIH Consensus grading criteria.

Older paediatric patient age is associated with higher probability of developing cGvHD; 44% probability in those older than 15 years, 30% probability in those aged 5 to 15 years, and less than 14% in those younger than 5 years.

The most important risk factor for the development of cGvHD is acute GvHD (Hauron et al 2023). Approximately 30% of cGvHD are de novo without any preceding aGvHD (Lee 2017).

2.1.3. Biologic features and pathogenesis

2.1.3.1. Acute GvHD

Acute GvHD is mainly characterized by mature donor T cell-mediated inflammatory disease.

2.1.3.2. Chronic GvHD

cGvHD is characterized by the activation of complex signaling pathways in both T and B cells, reduced levels of circulating regulatory B cells (Bregs) and CD4+ Tregs. Cytokine dysregulation has also been implicated through observations that high levels of interleukin (IL)-1β, IFNγ, and tumor necrosis factor (TNF)-α are associated with more severe cGvHD. These inflammatory cytokines then recruit and induce proliferation of additional immune effector cells, thereby perpetuating an adverse cycle of alloreactive tissue injury and inflammation.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

2.1.4.1. Acute GvHD

aGvHD usually presents early after engraftment, with a median time to onset (grade II-IV) of 20-25 days. The clinical manifestations are seen primarily in three organs:

- skin (maculopapular erythematous skin rash, erythroderma)
- liver (cholestasis, hyperbilirubinemia, and/or jaundice)

- upper and lower gastrointestinal tract (nausea, abdominal pain, vomiting, anorexia with weight loss, secretory diarrhea, GI bleeding and/or ileus)

The overall severity of aGvHD is graded from I (mild) to IV (life-threatening) according to the degree of involvement of the individual organs. The diagnosis and clinical staging are assessed using a comprehensive and systematic approach for the determination of aGvHD onset, confidence in the attribution of symptoms to aGvHD, and quantification of clinical severity of aGvHD in each target organ (The MAGIC criteria, Harris et al 2016, Schoemans et al 2018).

aGvHD is one of the leading causes of mortality post alloHSCT. The non-relapse mortality (NRM) has been reported to be 26% for grade III and 68% for grade IV aGvHD (Zecca et al 2018). Adult and paediatric patients with grade III-IV aGvHD have a high mortality risk with a 2-year survival rate of 27-35% (Khoury et al 2017).

2.1.4.2. Chronic GvHD

cGvHD is a major long-term complication after alloHSCT, occurring most frequently after 100 days post-transplant with a median time to onset reported as 162 days post-transplant.

cGvHD usually involves not only the epithelial target tissues affected in classic aGvHD (skin, liver, GI tract) but also additional organ systems including lungs, muscles, fascia, joints, genitalia, eyes, and nails. The signs and symptoms include rash, raised or discoloured skin, thickening or tightening of skin, dry mouth, yellow discoloration of skin/eyes dry eyes, shortness of breath, weight loss, difficulty swallowing, fatigue, and muscle weakness.

cGvHD is classified into mild, moderate, and severe based on degree and number of organs or sites involved according to standard criteria by 2014 NIH Chronic GvHD Diagnosis and Staging Consensus Recommendations (Jagasia et al 2015).

Moderate to severe cGvHD is the major cause of TRM and inferior OS following alloHSCT. Children with severe cGvHD experience a 10-year non-relapse mortality (NRM) rate of about 35%, compared with 4-5% among children with mild to moderate cGvHD (Inagaki et al 2015).

In addition, cGvHD adversely affects physical and functional well-being as well as quality of life of most of the patients who are otherwise cured for their underlying disease after HSCT (Lee 2017, Arai et al 2015).

2.1.5. Management

The optimal practice for paediatric GvHD prophylaxis and treatment is not clearly defined and varies across institutions, but corticosteroids are almost universally used in first-line treatment for acute and chronic GvHD in adult and paediatric patients.

Corticosteroids have detrimental effects in children such as weight gain, insulin resistance, proximal myopathy, hypertension, skin atrophy, bone resorption, femoral head avascular necrosis, immunosuppression with increased risk of infection and growth retardation (Hauron et al 2023). Corticosteroid withdrawal and/or avoidance are important to reduce potential steroid toxicity (Schacke et al 2002, Mazziotti, Giustina 2013). Although corticosteroids mitigate the allogeneic T-cell response, their impact on wound healing and tissue regeneration and on ameliorating tissue tolerance may in some contexts antagonize recovery from GvHD (Toubai, Maganeu 2020).

In patients transplanted for underlying **malignant diseases**, a key challenge in GvHD management is to reduce the severity of GvHD but still maintain the graft-versus-leukaemia (GvL) effect from the

donor T-cells to reduce the risk for relapse of the malignant disease. Thus, the goal is to reduce the GvHD reaction at the lowest cost of cure to maintain the GvL effect, but also to minimise the impact on immune reconstitution and infectious complications post alloHSCT (Wölfl et al 2022).

In contrast, the GvHD reaction does not have any beneficial effects in those patients who undergo alloHSCT for **non-malignant diseases** such as sickle cell disease, thalassemias, or inborn metabolic diseases, for which a GvL reaction is not needed. Thus, more aggressive approaches to GvHD management are seen in patients with non-malignant diseases since they do not benefit from GvHD/GvL effect (Lawitschka et al 2020). Compared to adults, paediatric patients are more likely to undergo allogeneic HSCT for a non-malignant disease (Hauron et al 2023).

The MAH states that there is a high unmet need for effective treatment options in (i) younger patients aged ≥ 28 days to <12 years with SR GvHD and in (ii) treatment-naïve patients aged ≥ 28 days to <18 years that could benefit from a steroid-sparing practice due to the risks associated with long-term corticosteroid exposure.

GvHD prophylaxis

GvHD prophylaxis is often based on suppressing the donor T-cell function using immunosuppression regimens such as a calcineurin inhibitor (CNI, cyclosporine A or tacrolimus) with or without a short course of methotrexate. There are no optimal or standard preventive methods for GvHD defined and treatments vary across institutions.

Other prophylactic regimens used in adults, but infrequently in children, include prednisone, tacrolimus, sirolimus, ATG, rituximab, cyclophosphamide, alemtuzumab, and anti-IL-2R antibodies.

2.1.5.1. Acute GvHD

Corticosteroids are the mainstay of aGvHD therapy, with a high inter-center variability in the starting dose of corticosteroids. High dose systemic corticosteroids (methylprednisolone 2 mg/kg/day or prednisone 2-2.5 mg/kg/day) is the standard initial treatment of grade II to IV aGvHD (Penack et al 2020, Gatza et al 2020).

Although details and definitions of corticosteroid refractoriness vary considerably, about one third to half of paediatric patients with aGvHD do not respond to upfront corticosteroid therapy. Second-line therapies are often considered if there is no response to corticosteroids after 2-7 days or if there is rapid progression within 48-72 h (Carlberg et al 2017, Gatza et al 2020, Verbeek et al 2022).

A major consequence of aGvHD in paediatric patients is the toxicity of corticosteroid therapy.

There is no consensus on the choice of optimal second-line therapy for paediatric aGvHD.

The varying response rates observed with the second-line agents are difficult to interpret due to differences in study designs (majority are retrospective and/or single-center studies), heterogeneity of study population, different age-groups, different underlying diagnoses, small sample size, varied criteria for steroid refractoriness, and lack of standardized endpoints.

Except for ruxolitinib, which is currently approved for the treatment of acute or chronic GvHD in adolescent patients 12 to <18 years with inadequate response to corticosteroids or other systemic therapies, there are no treatments approved in the EU for use in paediatric aGvHD.

2.1.5.2. Chronic GvHD

Systemic therapy is warranted in patients with moderate to severe cGvHD. Corticosteroids (prednisone 1 mg/kg/day) with or without a CNI is the standard of care in first line irrespective of the age (Hauron et al 2023). The addition of a CNI to corticosteroids does not increase the response rate but allows for a reduction in corticosteroid dosing which is of particular interest in children to reduce long-term side effects (Sobkowiak-Sobierajska et al 2022). Steroid-free practice is typically applied to less than 20% of patients with certain comorbidities and previous complications of HSCT (Moiseev et al 2020, Moiseev et al 2023).

In patients responding to corticosteroids, gradual tapering of prednisone is recommended to minimize the risk of infection and other toxicities, but immunosuppressive treatment in cGvHD is typically required on an average for 2 to 3 years (Inamoto et al 2011).

About 50% to 60% of paediatric patients develop corticosteroid-refractory or corticosteroid-dependent disease and require addition of another systemic therapy beyond systemic corticosteroids and CNIs within 2 years after initial therapy (Inamoto 2014). No standard therapy has been established for SR patients and a range of agents have been used off-label.

In a survey by EBMT, 52% of transplant centers confirmed using corticosteroid-free first-line treatments in moderate and severe chronic GvHD, the most commonly used steroid-free treatments involve CNIs, extracorporeal photopheresis (ECP), and ruxolitinib (Moiseev et al 2020).

Except for ruxolitinib, currently approved for the treatment of acute or chronic GvHD in adolescent patients 12 to <18 years with inadequate response to corticosteroids or other systemic therapies, there are no treatments approved in the EU for use in paediatric cGvHD.

2.2. About the product

Ruxolitinib is a Biopharmaceutical Classification System (BCS) class 1 compound, with high permeability, high solubility and rapid dissolution characteristics.

Ruxolitinib is an inhibitor of the Janus Kinases (JAKs) JAK1 and JAK2 and interferes with the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. Inhibition of JAK1/2 signaling is described to result in reduced proliferation of donor effector T cells, suppression of pro-inflammatory cytokine production in response to alloantigen, as well as impairment of antigen presenting cells (Socié, Ritz 2014, Spoerl et al 2014, Betts et al 2011).

2.3. Type of Application and aspects on development

With this application, the MAH is seeking approval for ruxolitinib in patients aged 28 days to less than 18 years old with acute or chronic GvHD. This application also supports the use of an oral solution for paediatric patients.

The initially sought indication is;

Jakavi is indicated for the treatment of patients aged 28 days to less than 18 years old with acute or chronic graft versus host disease (see section 5.1).

The initially proposed dosing is;

Table 2 Starting doses in acute and chronic graft versus host disease	
Age group	**Starting dose**
12 years old and above	10 mg orally twice daily
6 years to less than 12 years old	5 mg orally twice daily
28 days to less than 6 years old	4 mg/m^2 orally twice daily
These starting doses in GvHD can be administered using either the tablet for patients at or above 6 years old who can swallow tablets or the oral solution for patients under 12 years old.	

The finally agreed indication is:

- *Acute GvHD*

  Jakavi is indicated for the treatment of adults and paediatric patients aged 28 days and older 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 adults and paediatric patients aged 6 months and older with chronic graft versus host disease who have inadequate response to corticosteroids or other systemic therapies (see section 5.1).

The finally agreed dosing is:

Starting doses in acute graft versus host disease

Age group	Starting dose
12 years old and above	10 mg orally twice daily
6 years to less than 12 years old	5 mg orally twice daily
28 days to less than 6 years old	8 mg/m^2 orally twice daily

Starting doses in chronic graft versus host disease

Age group	Starting dose
12 years old and above	10 mg orally twice daily
6 years to less than 12 years old	5 mg orally twice daily
6 months to less than 6 years old	8 mg/m^2 orally twice daily

The clinical development program of ruxolitinib for the treatment of paediatric subjects with GvHD following alloHSCT includes two paediatric Phase I/II studies, F12201/REACH4 and G12201/REACH5 evaluating the pharmacokinetics, efficacy, and safety of ruxolitinib in addition to the dose determination for ruxolitinib in paediatric acute GvHD and chronic GvHD, respectively.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as an oral solution containing 5 mg/ml ruxolitinib as active substance.

Other ingredients are: propylene glycol (E1520), methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), sucralose (E955), anhydrous citric acid, strawberry dry flavour and purified water.

The product is available in amber glass bottles with white poplypropylene child-resistant screw cap closures. The finished product is co-packaged with one low density polypropylene press-in bottle adaptor (PIBA) equipped with plunger O-rings and two 1 ml polypropylene oral syringes as described in section 6.5 of the SmPC.

2.4.2. Active Substance

Jakavi 5 mg/ml oral solution contains the same active substance, ruxolitinib, as that used to manufacture the already authorised tablet presentations. The active substance is sourced from the same manufacturer, manufactured by the same process and released in accordance with the same specifications. Therefore, the applicant presented no new information in the active substance dossier part of to support this line extension application.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The composition of Jakavi oral solution is presented in **Error! Reference source not found.**. The product is a clear, colourless to light yellow solution for oral administration via the provided 1 mL graduated syringes. The bottle contains a total fill volume to allow for material left in the oral syringes during administration.

Jakavi tablets are already approved and available in 5 mg, 10 mg, 15 mg and 20 mg strengths. The oral solution (5 mg/mL) applied for in this line extension was developed to facilitate administration to paediatric patients (up to 12 years) as the tablets are not considered suitable.

The active substance is highly soluble and belongs to BCS Class I and is thus suited to formulation as an aqueous oral solution. The development considered various aspects like stability (physical and chemical), taste, microbial stability and safety of excipients as key parameters.

The excipients utilised in the proposed formulation well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards where relevant. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The concentrations are within usual ranges for oral solutions. Strawberry dry flavour is a commercially available flavouring premix not mentioned in any pharmacopoeia. Sweetening agents and flavour are included in the oral solution formulation to enhance palatability of the drug product for the intended patient population. The guideline on pharmaceutical development of medicines for paediatric has been taken into account.

In the initial submission, a major objection was raised as the levels of antimicrobial preservatives methyl and propyl parabenzoate had not been demonstrated to be as low as possible. In response, the applicant provided further data on the preservative effectiveness of batches manufactured with lower amounts of parabens, and also provided further justification of the proposed levels in the target patient population, which justifies the proposed levels in the formulation. Acceptable antimicrobial effectiveness has been shown with the proposed commercial formulation. The major objection was considered resolved.

The choice of excipients has been justified with respect to their function and safety for paediatric patients.

In clinical studies, the approved tablets, an extemporaneous capsule formulation and the oral solution were used. The applicant has provided acceptable *in vitro* dissolution data of the tablets and capsules to justify the claim that the formulations can be considered bioequivalent.

The primary packaging is a 70 ml amber glass bottles with white polypropylene child-resistant screw cap closures. Packs containing one bottle of 60 ml oral solution, two 1 ml polypropylene oral syringes and one low density polypropylene press-in bottle adapter equipped with plunger O-rings and printed with 0.1 ml graduation marks. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

A 1.0 mL oral dosing syringe with 0.1 mL graduations was selected to allow accurate deliver of the product over the intended dosing range. Uniformity of mass and dose accuracy of delivered doses has been demonstrated between 0.1 mL and 1.0 mL. The suitability of the oral syringes for multiple use was investigated over the anticipated in-use period of 60 days with 2 actuations per day for up to 120 dosing / dispensing cycles. Syringes were cleaned and dried between doses. No damage, discoloration, loss of printing adherence or change in resistance of the sliding force of the plunger was observed. Extractables/leachables studies have been performed with all materials in contact with the oral solution (primary packaging material, adaptor, syringes, tubes) and no safety concerns were identified.

The possibility to administer the oral solution through naso-gastric or gastric tubes has been evaluated. Considerations raised in the EMA Q&A on "Administration of oral immediate release medicinal products through enteral feeding tubes" have been acceptably addressed. Appropriate information on administration is included in the SmPC, section 4.2.

Manufacture of the product and process controls

The manufacturing process consists of 4 main steps: compounding, filtration, filling and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated on 3 consecutive production scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form including appearance (container and solution), identification (HPLC, UV-PDA), assay (HPLC), purity (HPLC), and microbial enumeration (Ph. Eur.).

The specification contains tests for relevant parameters and the associated limits have been justified. Reference is made to ICH, Ph. Eur. and EU guidelines where relevant. The justifications for not including tests for uniformity of mass of delivered doses, enantiomer, pH, residual oxygen, efficacy of antimicrobial preservation, absolute density, residual solvents and extractables/leachables are considered acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Screening data was presented for relevant samples. Based on the risk assessment and screening data, there is no risk to patients from elemental impurities and no specific controls are needed.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 16 batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 production scale batches of finished product stored for up to 18 months under various sets of conditions: refrigerated (5 ºC), 25 ºC/60% RH, 30 ºC/75% RH, and 40 ºC/75% RH. The batches were identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, degradation products and microbiology. In addition, enantiomer, pH and residual oxygen were also monitored. The analytical procedures used are stability indicating. No significant changes were observed at 5 and 25 ºC. A within specification increase in degradation products was observed at 30 ºC and at 40 ºC, while a within specification decrease in assay and increase in degradants was observed, appearance was out of specification within 3 months. A decrease in residual oxygen was also noted, correlating with an increase in oxidative degradants. The applicant originally proposed that the product be stored refrigerated. However, based on the stability data and considering end user convenience, less restrictive storage conditions were agreed within the procedure.

In addition, 2 batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. While the product is photosensitive, the study demonstrated that the amber bottle provides adequate protection from light.

A freeze and thaw cycle test was performed on samples from two batches. The stability samples were stored for four complete freeze and thaw cycles (-20 °C /ambient RH for 6 days, followed by 1 day at 25 °C/60% RH). Samples were pulled after 28 days and analysed. All quality attributes were within the specification after freeze and thaw cycle study. As a result, the initially proposed restriction "do not freeze" was removed from the SmPC during the procedure.

In-use stability data was provided for 2 batches. The study was conducted over 60 days with an intermediate time point of 30 days for the 25 °C/60% RH storage condition and with two intermediate time points of 15 and 30 days for the 30 °C/75% RH storage condition. No significant changes to any quality attributes were observed.

Based on available stability data, the proposed shelf-life of 24 months with the restriction "do not store above 30 °C" as stated in the SmPC (section 6.3) is acceptable. After opening the product should be used within 60 days.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The proposed levels of antimicrobial preservatives have been justified and the storage conditions have been amended for patient convenience. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

No new non-clinical data was submitted with this application which is considered acceptable.

All prior non-clinical data for ruxolitinib has been reviewed in previous procedures related to Jakavi and no re-assessment of the non-clinical data has been performed although the previous evaluation, especially the juvenile toxicity study, was considered in light of the current proposal to widen the paediatric age span to include patients from 28 days of age.

A juvenile toxicity study in rats was submitted previously and assessed and approved with the type II variation EMEA/H/C/002464/II/0040 in 2019.

The information in sections 4.6 and 5.3 of the SmPC remain unchanged.

2.5.2. Ecotoxicity/environmental risk assessment

An ERA dated 13 January 2021, which includes the whole paediatric population for the GvHD indication, has been included in the submission. This ERA was previously assessed in the procedure for the first GvHD submission which included patients aged 12 years or older (EMEA/H/C/002464/II/0053).

It is concluded that the total PECsw for all approved indications remains below the trigger value and no further steps are taken. Previous assessment has demonstrated ruxolitinib not be a persistent, bioaccumulative and toxic substances (PBT) substance.

Table 3. Summary of main study results

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	logP = 2.3 – 2.6 (at pH 4) logP = 2.3 – 2.4 (at pH 7) logP = 3.6 – 4.0 (at pH 9)	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	< 4,5	not B
	BCF	N/A	-
Persistence	DT50 or ready biodegradability		not P
Toxicity	NOEC or CMR		not T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0,008	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N

2.5.3. Discussion on non-clinical aspects

Ruxolitinib PEC $_{surfacewater}$ value is below the action limit of 0.01 µg/L and is not a PBT substance as log K_{ow} does not exceed 4.5. Therefore ruxolitinib is not expected to pose a risk to the environment.

Assessment of paediatric data on non-clinical aspects

A juvenile toxicity study in rats was previously submitted, assessed and approved with the type II variation EMEA/H/C/002464/II/0040 in 2019. The ages of the rats in the juvenile toxicity study are considered to cover the human equivalents of new-borns, 1 years and 2-3 years of age, respectively and the final treatment day is considered to reflect adolescents. In the rat juvenile toxicity studies, growth and bone effects were noted. The effects were generally more severe when administration was initiated earlier in the postnatal period. Other than bone development, the effects of ruxolitinib in juvenile rats were similar to those in adult rats. Juvenile rats are more sensitive than adult rats to ruxolitinib toxicity.

2.5.4. Conclusion on the non-clinical aspects

No new non-clinical data was submitted for the current application. This is considered acceptable. However, the impairment of bone development in rats is addressed in the context of clinical safety (see Clinical Safety).

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study Code	Study type	Study description	Study population (number of subjects exposed)	Ruxolitinib Dose & Formulation	PK sampling plan
Acute GvHD					
Study F12201	PK, activity and safety of ruxolitinib	Open label, Single arm, multi center, Phase I/II study	Subjects with either grade II-IV treatment naive acute GvHD or grade II-IV SR acute GvHD aged ≥ 28 days to < 18 years (N=45) **Group 1:** ≥ 12y to < 18y (N= 18) **Group 2:** ≥ 6y to < 12y (N= 12) **Group 3:** ≥ 2y to < 6y (N= 15) **Group 4:** ≥ 28 days to < 2y (N= 0)	All pediatric subjects: ruxolitinib as a 5 mg tablet or as an oral pediatric formulation b.i.d. daily for 24 weeks **Group 1:** 10 mg b.i.d. **Group 2**: 5 mg b.i.d. **Group 3**: 4 mg/m² b.i.d.	• **Extensive PK sampling:** for first 5 subjects in Group 1 and all Phase I pediatric subjects in Group 2 and 3 with blood samples collected on days 1, 7, 14 and 28 at pre-dose. • For post-dose samples: Day 1: 0.5 h, 1.0 h, 1.5 h (±15 min), 2.0 h, 4.0 h, 6.0 h and 9 h (±1 h). Days 7, 14 and 28: 2.0 h (±15 min) • **Sparse PK sampling:** for all the other Phase II pediatric subjects with blood samples collected at pre-dose and post-dose 2 h (± 15 min) on Days 28, 56, 84, 140 and 168.
Study C2301	Efficacy, safety and PK of ruxolitinib in subjects with acute GvHD after a single dose and at steady state exposure	Randomized, open label, crossover , multi center, Phase III study of ruxolitinib vs. BAT	Subjects with Grade II-IV steroid-refractory acute GvHD aged 12 or older (N=309). Including 5 adolescent subjects randomized to ruxolitinib arm	10 mg b.i.d. daily (two 5 mg tablets)	• **Extensive PK' sampling**: for first 25 adult and all adolescent subjects with blood samples collected on days 1 and 7 at pre-dose and 7 post-dose samples (0.5 h, 1.0 h, 1.5 h, 2.0 h, (±15 min), 4.0 h, 6.0 h and 9 h (±1 hr). Thereafter one pre-dose and one post-dose 2 h (± 15 min) on days 14 and 28, and further on days 42, 56, 96 and 168 • **Sparse PK sampling**: for all other adult subjects with samples collected at pre-dose and post-dose 2 h (± 15 min) on Days 1, 7, 14, 21, 28, 42, 56, 96 and 168.

Study Code	Study type	Study description	Study population (number of subjects exposed)	Ruxolitinib Dose & Formulation	PK sampling plan
Chronic GvHD					
Study G12201	PK, activity and safety of ruxolitinib	Open label, Single arm, multi center, Phase II study	Subjects with either moderate or severe treatment-naive chronic GvHD or SR chronic GvHD. aged ≥ 28 days to < 18 years (N=46*) **Group 1:** ≥ 12y to < 18y (N= 22) **Group 2:** ≥ 6y to < 12y (N= 16) **Group 3:** ≥ 2y to < 6y (N= 7) **Group 4:** ≥ 28 days to < 2y (N= 0)	All subjects: ruxolitinib as a 5 mg tablet or as an oral pediatric formulation b.i.d. daily for 156 weeks **Group 1:** 10 mg b.i.d. **Group 2**: 5 mg b.i.d. **Group 3**: 4 mg/m² b.i.d.	• Sparse PK sampling for first 5 subjects in Groups 1, 2 and 3 with blood samples collected on days 1, 8, 15 and 22 at pre-dose. • For post-dose samples: Day 1: 0.5 h (±15 min), 2.0 h (±15 min), 6.0 h (±2 h)
Study D2301	Efficacy, safety and PK of ruxolitinib in subjects with chronic GvHD after a single dose and at steady state exposure	Randomized, open label, crossover , multi center, Phase III study of ruxolitinib vs. BAT	Subjects with moderate or severe steroid refractory corticosteroid-refractory chronic GvHD aged 12 y or older (N=329). Including 4 adolescent subjects.	10 mg b.i.d. daily (two 5 mg tablets)	• **Extensive PK sampling**: for first 8 adult and 4 adolescent subjects on days 1 and 15 of Cycle 1: pre-dose (0 h), post-dose (0.5 h, 1 h, 1.5 h (±15 min), 4 h, 6 h, 9 h (±1 h). At Cycle 2, 7 and 39, one pre-dose (0 h) and one-post dose 1.5 h (±15 min). • **Sparse PK sampling**: for all other subjects with samples collected at pre-dose and post-dose 1.5 h (± 15 min) on Day 1, Day 15 of Cycle 1, and Day 1 of Cycle 2, 7 and 39.

SR: steroid refractory; BAT: Best available therapy; EOT: End of treatment

* A total of 46 subjects were enrolled; of these, 45 subjects were analyzed as 1 subject was enrolled and treated beyond local regulatory requirements and excluded from all summary-level analyses. The demographic and safety data from this single subject is presented separately in [Study G12201 Primary analysis CSR-Section 12.7].

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The existing tablet formulation was developed as an uncoated immediate release solid oral formulation (5 mg, 10 mg, 15 mg and 20 mg). Two paediatric formulations, an extemporaneous solution from hard non-gelatin capsule (HNC) (hereafter referred to as 'capsule') and an oral solution were developed to support the treatment of acute and chronic graft versus host disease (GvHD) in paediatric subjects. The capsule formulation was used in Study F12201 only and is not planned for commercialization.

The oral solution was developed as 5 mg/mL strength considering the need for an age-appropriate formulation and flexible dosing in the target subject populations. Excipients used in the paediatric formulations are not expected to affect gastrointestinal transition, absorption, *in vivo* solubility or *in vivo* stability of the drug substance.

In the paediatric studies F12201 and G12201, the tablet was used in most subjects aged 6-18 years who were able to swallow tablets. Capsule or oral solution were used in subjects below the age of 12 years. Capsule/oral solution were used in Study F12201 and the oral solution was used only in Study G12201. Study F12201 used the 1 mg, 1.5 mg and 2.5 mg capsule.

Table 4. Overview of formulations evaluated in the ruxolitinib paediatric development program

Table	Study Type	Population	Dose and Formulations used
F12201 (REACH 4)	Phase I/II	Pediatric subjects from ≥28 Days to <18y with either treatment naïve acute GvHD grades II-IV or grade II-IV steroid-refractory acute GvHD following allogeneic HSCT (N=45)	- 5 mg uncoated tablets, - extemporaneous solution from 1, 1.5, 2.5 mg HNC - 5 mg/mL oral solution
G12201 (REACH 5)	Phase II	Pediatric subjects from ≥28 Days to <18y of age with moderate or severe treatment-naïve or SR chronic GvHD following allogeneic HSCT (N=45)	- 5 mg uncoated tablets - 5 mg/mL oral solution

Methods

Bioanalysis

The determination of ruxolitinib in human plasma was performed by using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

Pharmacokinetic data analysis

The PK of ruxolitinib was evaluated in paediatric subjects with acute and chronic GvHD according to non-compartmental as well as population PK approaches. In subjects with extensive PK sampling on Day 1 (Study F12001), PK parameters of ruxolitinib were calculated by non-compartmental methods. The following parameters were derived, when possible; AUC_{last}, AUC_{inf}, AUC_{0-12}, C_{max}, C_{trough}, T_{max}, $T_{1/2}$, CL/F and Vz/F.

Population PK analysis

A full GvHD model describes the PK of ruxolitinib in all subjects with acute or chronic GvHD and was described as a 2-compartment model with first-order absorption process, a lag-time of 0.148 h and a linear elimination. Covariates included in the full model were cGvHD effect on Ka, Cl/F and Vc/F, BSA effect on Cl/F and Vc/F, lower GI effect on Vp/F. The lower GI effect on Ka, included in the initial adult-

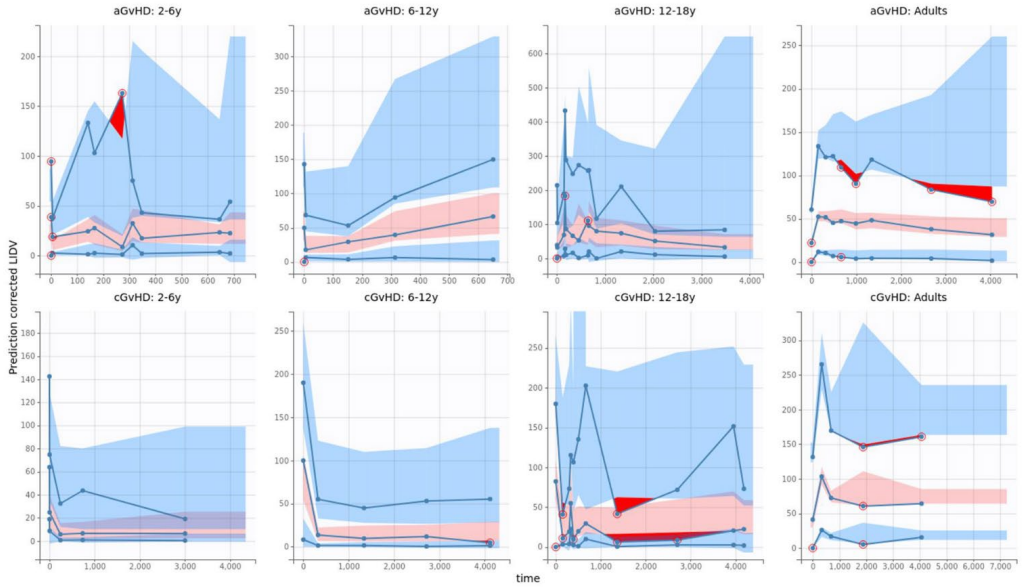
adolescent popPK model, was removed during model development. Chronic GvHD appears to have a strong impact on Ka, even stronger than in adults and adolescents alone. In the full model, impact of fluconazole administration on Cl/F was added as a subject level characteristic. The final full model parameter estimates are presented in Table 5.

Table 5 Population estimates of the final full GvHD model

	Estimates			Inter-individual variability (IIV)		
Parameter	**Mean**	**SE**	**RSE**	**Mean**	**SE**	**RSE**
Tlag (h)	0.148	0.034	22.88	0.932	0.139	14.934
Ka (h^{-1})	4.057	1.358	33.465	1.566	0.170	10.862
Chronic GvHD flag on ka	0.714	0.376	52.602	-	-	-
Cl (L/h)	5.946	0.7	11.747	0.479	0.021	4.403
Chronic GvHD flag on Cl/F	-0.184	0.056	30.231	-	-	-
Fluconazole flag on Cl/F	-0.34	0.066	16.525	-	-	-
BSA/1.83 on Cl/F	0.593	0.120	20.22	-	-	-
Vc/F (L)	16.416	1.475	8.984	0.307	0.025	8.250
Chronic GVHD flag on Vc/F	-0.161	0.046	28.614	-	-	-
	Estimates			**Inter-individual variability (IIV)**		
Parameter	**Mean**	**SE**	**RSE**	**Mean**	**SE**	**RSE**
BSA/1.83 on Vc/F	1.510	0.096	6.347	-	-	-
Q (L)	11.59	0.590	5.094			
Vp/F	1.654	1.596	96.492	5.694	0.578	10.149
Involvement of lower GI at baseline, on Vp/F	4	1.014	25.368	-	-	-
Correlation between Vc/F and Cl/F	0.670	0.096	14.359			
Residual error	0.496	0.008	1.514			

Model diagnostics, represented by prediction corrected Visual Predictive Check, displayed reasonable description of observed data.

Figure 1 Final prediction corrected visual predictive check by age and indication.



Concentration (LIDV) in ng/mL is presented on y-axis, time in hours is presented on x-axis.
The observed median, 10th and 90th percentiles are presented, with 90% confidence intervals of the simulated median (red area), 10th and 90th percentiles (blue areas) displayed.

Physiologically-based pharmacokinetic modelling

A GvHD adult ruxolitinib PBPK model was used within the Simcyp paediatric simulator to predict the exposure of ruxolitinib in GvHD paediatric subjects, by incorporating the ontogeny of clearance pathways for CYP2C9 and CYP3A4 (using the Upreti Wahlstrom 2016 ontogeny), as well as anatomical and physiological changes with age. The ruxolitinib PK data from older paediatric population with GvHD aged from ≥2 to <18 years was used in identifying starting doses in subjects with GvHD under the age of 2 years. In Study F12201 and G12201, the PK of ruxolitinib was more variable in paediatric subjects with GvHD than in adults and the number of paediatric subjects was limited. In general, the values for Cmax, AUClast and Ctrough were in the range of what was observed in adults, although the averages were lower.

Absorption

Ruxolitinib is a Biopharmaceutical Classification System (BCS) class 1 compound, with high permeability, high solubility and rapid dissolution characteristics. In clinical studies, ruxolitinib was rapidly absorbed after oral administration with maximal plasma concentration (C_{max}) achieved approximately 1 hour post-dose. For the tablet formulation, there was no clinically relevant change in the pharmacokinetics of ruxolitinib upon administration with a high-fat meal. The mean C_{max} was moderately decreased (24%) while the mean AUC was nearly unchanged (4% increase) on dosing with a high-fat meal.

Bioequivalence

No dedicated bioavailability/bioequivalence (BA/BE) study was conducted with the two paediatric formulations compared to the approved tablet formulation.

Dissolution of the three formulations

As ruxolitinib is a BCS Class I compound, formulation related differences are not expected. Clinical pharmacokinetic data from multiple studies part of the original Marketing Authorization application (MAA) collectively indicated that ruxolitinib has near-complete oral absorption and that the different solid-dose formulations evaluated are bioequivalent. Also, ruxolitinib has linear PK beyond the therapeutic range.

The tablets were approved based on all tablet strengths having more than 85% of drug substance dissolved within 15 minutes (in pH 1.0, pH 4.5 and pH 6.8 dissolution media) meeting the EMAs "very rapid dissolving" criteria (EMA 2010) and confirming the BCS I designation.

Study F12201

Study F12201 was an open-label, Phase I/II, single-arm, multi-center study to investigate the PK, activity and safety of ruxolitinib when added to the subject's immunosuppressive regimen in infants, children, and adolescents aged ≥28 Days to <18 y with either grade II-IV treatment-naïve acute GvHD or grade II-IV steroid refractory acute GvHD. Forty-five subjects were treated in this study and grouped according to their age as follows: Group 1 included 18 subjects ≥ 12 to < 18 years (10 mg b.i.d.), Group 2 included 12 subjects ≥ 6 to < 12 years (5 mg b.i.d.) and Group 3 included 15 subjects ≥ 2y to < 6y (4 mg/m2 b.i.d.). No subjects were enrolled in Group 4 ≥ 28 days to < 2 years.

Table 6. PK parameters by age group and dose formulation (Pharmacokinetic Analysis Set)

		≥12y - <18y	≥6y - <12y			≥2y - <6y			
Parameter	**Statistics**	**RUX 10mg b.i.d. Tablet N=14**	**RUX 5mg b.i.d. Tablet N=9**	**RUX 5mg b.i.d. Capsule N=2**	**All Subjects N=11**	**RUX 4mg/m² b.i.d. Capsule N=7**	**RUX 4mg/m² b.i.d. Liquid N=8**	**All Subjects N=15**	**All Subjects N=40**
AUClast (ng*hr/mL) (Day 1)	n	5	8	2	10	7	8	15	30
	Geo-mean	252	372	154	311	239	259	249	269
	Geo-CV%	187	58.6	58.1	70.2	65.3	53.6	56.9	78.2
	Median	358	398	165	337	231	223	231	267
	Min-Max	45.1 - 1070	123 - 676	105 - 225	105 - 676	94.8 - 561	153 - 702	94.8 - 702	45.1 - 1070
Cmax (ng/mL) (Day 1)	n	5	8	2	10	7	8	15	30
	Geo-mean	66.1	105	49.4	90.3	61.2	66.5	64.0	72.2
	Geo-CV%	170	71.4	45.7	74.6	81.1	60.8	67.5	83.8
	Median	102	107	51.8	72.5	51.4	62.0	58.4	69.4
	Min-Max	9.89 - 184	38.1 - 257	36.3 - 67.2	36.3 - 257	31.1 - 229	35.9 - 193	31.1 - 229	9.89 - 257
Ctrough (ng/ml) (Day 7)	n	7	6	2	8	6	8	14	29
	Geo-mean	9.27	9.75	1.71	6.31	6.18	3.99	4.79	6.07
	Geo-CV%	379	256	1.2	266	196	277	225	252
	Median	6.08	13.4	1.72	5.62	3.44	3.89	3.44	4.33
	Min-Max	0.00 - 108	1.26 - 48.8	1.70 - 1.73	1.26 - 48.8	0.00 - 44.3	0.00 - 27.1	0.00 - 44.3	0.00 - 108
T1/2 (h)	n	2	5	2	7	5	5	10	19
	Median	1.36	1.66	1.50	1.58	2.12	1.58	1.85	1.58
	Min-Max	1.07 - 1.65	1.31 - 2.12	1.44 - 1.57	1.31 - 2.12	1.24 - 2.58	0.998 - 3.40	0.998 - 3.40	0.998 - 3.40

n=number of subjects with corresponding evaluable PK parameters

Comparison of bioavailability between capsules and tablets

In Study F12201, out of the 11 subjects in the ≥6y to <12y age group, 9 subjects were treated with the tablet, and 2 subjects were treated with the capsule. In the ≥6y to <12y age group receiving 5 mg b.i.d, the exposure in terms of C_{max} and AUC_{last} was approximately 2-fold lower in subjects receiving the capsule as compared to subjects receiving the tablet formulation, but this should be interpreted with caution as only 2 subjects received the capsule formulation and PK variability is known to be high in GvHD subjects.

Comparison of bioavailability between oral solution and tablets

The oral solution is a ready to use formulation with the drug substance in the solubilized state. In Study F12201, a direct comparison of the PK between the tablet and the oral solution was not done as no subjects received these formulations within the same age group.

Comparison of bioavailability between oral solution and capsules

In Study F12201, out of the 15 subjects in the ≥2y to <6y age group, 8 subjects were treated with the oral solution, and 7 subjects were treated with the capsule. In this age group, the exposure in terms of C_{max}, AUC_{last} and C_{trough} was similar between subjects receiving the capsule and subjects receiving the oral solution.

The median T_{max} is 1.5 h, 1.5 h and 1 h for the tablet, capsule and oral solution, respectively.

Influence of food

No dedicated food effect studies were conducted with the two paediatric formulations (capsule and oral solution) to support this submission.

The results from a food effect study (with tablet formulation) indicated that the effect of food on the ruxolitinib exposure profile is not clinically relevant and ruxolitinib administered as tablets may be administered either with or without food.

Ruxolitinib was administered regardless of food in both paediatric studies (Study F12201 and Study G12201). Subjects (or caregivers) were asked if the subject was fasted for 2 hours or not at the time of ruxolitinib administration and this was documented in the CRF of each study.

Distribution

Based on population PK analysis, volume of distribution is similar in adult and paediatric subjects.

Elimination

Based on population PK analysis, clearance is similar in adult and paediatric subjects.

Dose proportionality and time dependencies

Not applicable

Special populations

Special population predictors such as renal impairment, hepatic impairment, ethnicity, and gender were graphically assessed in the population PK analysis with no apparent influence.

Body size influence on PK is adequately captured by body surface area.

Exposure reference range

The adult reference range for aGvHD was defined as the 5th to 95th percentile adult exposure range as observed in the acute GvHD study (C2301) on Day 1. For AUC, the 5th and 95th percentile have a value of 121 and 1530 ng*h/mL, respectively. For Cmax, the 5th and 95th percentile have a value of 55.4 and 258 ng/mL, respectively.

The adult reference range for aGvHD was defined as the 5th to 95th percentile adult exposure range as observed in the chronic GvHD study (D2301) on Day 1. For AUC, the 5th and 95th percentile have a value of 313 and 1400 ng*h/mL, respectively. For Cmax, the 5th and 95th percentile have a value of 67.8 and 312 ng/mL, respectively.

Exposure in target population

Study F12201

Table shows predicted day 1 PK parameters in this study based on the Population PK analysis ("Full PK model").

Table 7 Predicted Day 1 PK parameters for subjects in study F12201

		Age Group		
PK Parameter	**Summary statistic**	**≥2y - <6y**	**≥6y - <12y**	**≥12y - <18y**

AUC0-12 (h*ng/mL)	mean	274	354	646
	median	203	324	683
	[Min, Max]	[95.0, 762]	[156, 632]	[62.2, 1186]
AUC0-9 (h*ng/mL)	mean	246	321	571
	median	179	308	593
	[Min, Max]	[94.1, 656]	[150, 512]	[40.1, 1011]
Cmax (ng/mL)	mean	69.7	97.8	151
	median	58.6	106	151
	[Min, Max]	[5.07, 158]	[42.3, 134]	[12.0, 243]
Tmax (h)	median	2	2	2

Study G12201

Day 1 PK parameters of Cmax (and corresponding Tmax), AUC0-12 and AUC0-9 (to match the observed sampling scheme in study D2301) were predicted based on the Population PK analysis ("Full PK model").

Table 8 Predicted Day 1 PK parameters for subjects in study G12201

		Age Group		
PK Parameter	**Summary Statistic**	**≥2y - <6y**	**≥6y - <12y**	**≥12y - <18y**
AUC0-12 (h*ng/mL)	mean	204	497	633
	median	200	460	633
	[Min,Max]	[151, 288]	[123, 797]	[185, 1178]
AUC0-9 (h*ng/mL)	mean	188	438	563
	median	193	408	556
	[Min,Max]	[136, 261]	[122, 661]	[170, 999]
Cmax (ng/mL)	mean	61.6	123	161
	median	58.1	118	162
	[Min,Max]	[39.2, 86.5]	[51.2, 190]	[43.2, 242]
Tmax (h)	median	1	1	1

Exposure simulations based on population pharmacokinetic modelling

Alternative dosing regimen from 4 to 10 mg/m2 as well as flat doses of 5 BID that would lead to similar exposure across all age groups were simulated using the full popPK model. The full popPK model for ruxolitinib in paediatric and adult patients with acute or chronic GvHD was updated to include CYP ontogeny functions for CYP3A4 and CYP2C9 which are the main enzymes responsible for the metabolism of ruxolitinib. The CYP3A4 ontogeny function proposed by Upreti and Wahlstrom 2016 suggests that CYP3A4 maturation increases from an early age to 2 years old and exceeds adult level between 0.1 and 11 years. CYP2C9 maturation increases from birth and reaches adult levels around 2 years old (as reported in the Simcyp Simulator v21; Upreti and Whalstrom 2016).

The simulations are presented below.

Table 9 Summary statistics of simulated ruxolitinib PK parameters (Cmax and AUClast) for acute GvHD patients aged 2-<12 years by dose including the proportion of patients within the adult reference range

		Age group			
		2-6y		6-12y	
Dose level		AUClast D1 (h.ng/mL)	Cmax D1 (ng/mL)	AUClast D1 (h.ng/mL)	Cmax D1 (ng/mL)
4mg/m2	Mean (SD)	248 (141)	106 (48.1)	346 (167)	132 (52.9)
	Median	211	102	310	129
	Q1-Q3	145 - 306	74.4 - 134	218 - 440	95.6 - 163
	Min-Max	23.2 - 947	5.36 - 357	61.8 - 1090	20.0 - 309
	% in ref. range	85.7%	84.6%	97.6%	91.4%
8mg/m2	Mean (SD)	501 (284)	210 (95.0)	685 (349)	263 (111)
	Median	432	210	605	252
	Q1-Q3	283 - 648	140 - 264	434 - 855	191 - 331
	Min-Max	82.7 - 1570	19.0 - 600	124 - 2420	33.9 - 806
	% in ref. range	98.9%	71.2%	96.6%	51.8%
10mg/m2	Mean (SD)	613 (333)	263 (114)	899 (456)	338 (144)
	Median	539	257	786	325
	Q1-Q3	362 - 795	185 - 323	545 - 1160	242 - 425
	Min-Max	58.5 - 2230	12.8 - 802	50.4 - 3250	17.0 - 828
	% in ref. range	98.0%	48.1%	90.0%	29.4%
5mg flat	Mean (SD)	465 (258)	192 (83.1)	407 (205)	157 (63.3)
	Median	403	184	349	151
	Q1-Q3	275 - 604	138 - 242	260 - 516	112 - 197
	Min-Max	45.1 - 1540	11.3 - 545	55.4 - 1680	12.9 - 398
	% in ref. range	98.0%	78.5%	98.5%	89.5%

Reference range is 5-95% of observed aGvHD adult NCA parameters
AUClast is defined as AUC0-9h

Table 10 Summary statistics of simulated ruxolitinib PK parameters (Cmax and AUClast) for chronic GvHD patients aged 2-<12 years by dose including the proportion of simulations within the adult reference range

		Age group			
		2-6y		6-12y	
Dose level		AUClast D1 (h.ng/mL)	Cmax D1 (ng/mL)	AUClast D1 (h.ng/mL)	Cmax D1 (ng/mL)
4mg/m2	Mean (SD)	299 (160)	138 (52.1)	425 (193)	170 (55.7)
	Median	256	131	383	164
	Q1-Q3	179 - 390	102 - 169	281 - 536	129 - 206
	Min-Max	57.2 - 1170	18.1 - 396	95.5 - 1180	42.9 - 357
	% in ref. range	38.6%	94.4%	67.0%	97.0%
8mg/m2	Mean (SD)	581 (290)	268 (96.1)	869 (419)	349 (121)
	Median	527	256	799	330

		Age group			
		2-6y		6-12y	
Dose level		AUClast D1 (h.ng/mL)	Cmax D1 (ng/mL)	AUClast D1 (h.ng/mL)	Cmax D1 (ng/mL)
	Q1-Q3	349 - 745	201 - 324	549 - 1100	266 - 417
	Min-Max	118 - 1820	31.3 - 648	216 - 3350	86.0 - 900
	% in ref. range	79.8%	71.3%	89.6%	42.6%
10mg/m2	Mean (SD)	741 (386)	346 (129)	1060 (498)	423 (139)
	Median	652	324	967	411
	Q1-Q3	446 - 945	257 - 413	663 - 1340	326 - 504
	Min-Max	117 - 2690	50.5 - 939	289 - 3350	97.3 - 1010
	% in ref. range	86.6%	44.9%	77.3%	20.5%
5mg flat	Mean (SD)	554 (294)	259 (90.4)	514 (242)	206 (70.6)
	Median	490	254	459	199
	Q1-Q3	325 - 703	199 - 312	327 - 658	158 - 243
	Min-Max	102 - 2070	23.0 - 588	124 - 1740	36.3 - 483
	% in ref. range	75.3%	73.8%	77.8%	91.2%

Reference range is 5-95% of observed aGvHD adult NCA parameters
AUClast is defined as AUC0-9h

Table 11 Summary statistics of simulated ruxolitinib AUClast for acute GvHD patients aged 28d-<2y by dose including the proportion of simulated patients within the adult reference range.

		Age group				
Dose level		1-2mo.	2-3mo.	3-6mo.	6mo.-1y	1-2y
4mg/m2	Mean (SD)	135 (76.8)	132 (75.2)	140 (88.4)	155 (87.7)	192 (113)
	Min-Max	29.2 - 383	12.6 - 567	24.3 - 798	13.1 - 561	30.9 - 1150
	% in ref. range	47.4%	47.4%	45.4%	51.2%	68.8%
6mg/m2	Mean (SD)	195 (111)	206 (119)	201 (118)	238 (141)	276 (159)
	Min-Max	32.4 - 646	24.7 - 718	19.8 - 709	26.6 - 860	16.8 - 1380
	% in ref. range	66.3%	70.0%	70.9%	80.5%	90.1%
8mg/m2	Mean (SD)	268 (162)	259 (154)	280 (160)	313 (187)	372 (220)
	Min-Max	18.0 - 1070	25.7 - 1290	16.2 - 893	39.5 - 1120	18.9 - 1490
	% in ref. range	86.3%	85.8%	91.1%	92.1%	94.2%
10mg/m2	Mean (SD)	319 (175)	326 (190)	338 (200)	381 (206)	465 (256)
	Min-Max	15.1 - 1020	34.4 - 1040	50.1 - 1230	38.6 - 1440	35.6 - 2010
	% in ref. range	95.7%	95.2%	95.4%	98.1%	98.1%

Reference range is 5-95% of observed aGvHD adult NCA parameters
AUClast is defined as AUC0-9h

Table 12 Summary statistics of simulated ruxolitinib AUClast for chronic GvHD patients aged 28d-<2y by dose including the proportion of simulated patients within the adult reference range.

		Age group				
Dose level		**1-2mo.**	**2-3mo.**	**3-6mo.**	**6mo.-1y**	**1-2y**
4mg/m2	Mean (SD)	167 (93.3)	169 (89.7)	165 (90.6)	208 (117)	231 (123)
	Min-Max	19.6 - 556	36.6 - 541	25.7 - 548	43.2 - 749	51.3 - 666
	% in ref. range	7.1%	6.4%	8.5%	18.4%	21.7%
6mg/m2	Mean (SD)	250 (140)	259 (139)	273 (158)	311 (161)	348 (178)
	Min-Max	58.4 - 811	57.0 - 1030	69.8 - 995	70.4 - 912	82.1 - 1120
	% in ref. range	29.7%	30.0%	34.2%	42.5%	47.9%
8mg/m2	Mean (SD)	341 (180)	339 (184)	348 (184)	442 (229)	466 (268)
	Min-Max	68.4 - 982	68.7 - 1240	27.4 - 1020	25.2 - 1410	94.3 - 2330
	% in ref. range	49.1%	48.6%	49.5%	66.3%	62.5%
10mg/m2	Mean (SD)	420 (228)	411 (225)	426 (241)	516 (273)	615 (319)
	Min-Max	101 - 1380	115 - 1370	29.0 - 1780	110 - 1400	153 - 1880
	% in ref. range	60.6%	59.7%	57.3%	71.7%	81.6%

Reference range is 5-95% of observed cGvHD adult NCA parameters
AUClast is defined as AUC0-9h

Exposure simulations based on physiologically based pharmacokinetic modelling

The predicted exposures subjects 28 days to <2 years were based on PBPK modelling. The exposure predictions, in terms of AUC and Cmax when receiving a dose of 4 mg/m^2 b.i.d. are reported in Table 13.

Table 13. PBPK model simulated ruxolitinib exposure at 4 mg/m2 b.i.d. in GvHD paediatric subjects <2 years old

Study	**Acute GvHD**				**Chronic GvHD**			
Day[1]	**Day 1**		**Day 56**		**Day 1**		**Day 168**	
Age at start of treatment (months)	**Cmax (ng/mL)**	**AUC12 (ng/mL.h)**	**Cmax (ng/mL)**	**AUC12 (ng/mL.h)**	**Cmax (ng/mL)**	**AUC12 (ng/mL.h)**	**Cmax (ng/mL)**	**AUC12 (ng/mL.h)**
1	105 (30)	460 (48)	86.0 (32)	371 (54)	159 (32)	514 (47)	119 (34)	380 (54)
3	91.5 (30)	394 (48)	84.6 (32)	366 (54)	151 (32)	473 (46)	124 (34)	396 (54)
6	82.5 (30)	358 (47)	82.0 (33)	357 (54)	143 (32)	444 (46)	129 (33)	409 (54)
12	75.8 (31)	328 (47)	80.2 (33)	349 (54)	134 (33)	414 (45)	132 (33)	420 (54)
22	71.4 (31)	306 (46)	77.0 (33)	332 (54)	128 (33)	389 (45)	131 (33)	409 (54)

Simulated PK parameters are presented as geometric mean (CV%)

[1]The simulated trials consisted of 10 trials of 10 subjects (n=100) with 50% of female. The virtual population used was the Sim-Paediatric population using the Upreti CYP3A4 ontogeny (*i.e.,* Sim-Paediatric-Upreti population file). Ruxolitinib was administrated as multiple b.i.d. oral doses (mg/m^2) for 2 months (d1-56) in acute GvHD and 6 months (d1-168) in chronic GvHD.

Pharmacokinetic interaction studies

N/A

Pharmacokinetics using human biomaterials

N/A

2.6.2.2. Pharmacodynamics

Mechanism of action

Ruxolitinib is an inhibitor of the Janus Kinases (JAKs) JAK1 and JAK2 and interferes with the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. Inhibition of JAK1/2 signaling is described to result in reduced proliferation of donor effector T cells, suppression of pro-inflammatory cytokine production in response to alloantigen, as well as impairment of antigen presenting cells (Socié, Ritz 2014, Spoerl et al 2014, Betts et al 2011).

Primary and Secondary pharmacology

N/A

2.6.3. Discussion on clinical pharmacology

Methods

The methods for analysing ruxolitinib were previously validated and found acceptable. The within study validation was also adequate.

Population PK analysis

Population PK model-predicted exposures are used to support the dosing recommendation in paediatric subjects, thus it is of importance that the population PK model can adequately describe the paediatric data. Two popPK models were developed in parallel, one based on paediatric-only data and one based on a pooled dataset will all GvHD subjects (full model). Both models gave similar results, and the full was used to predict exposure in GvHD subjects 2-18 years of age. The use of the full model is supported since the pooled dataset provide additional information.

In the response to questions, the MAH provided dose predictions based on the full popPK model with CYP3A4 and CYP2C9 ontogeny functions. The CYP ontogeny functions were based on the Upreti and Wahlstrom 2016 functions, which are commonly used ontogeny functions and thus accepted. The revised popPK model describe available PK data reasonably well.

Physiologically-based pharmacokinetic modelling

PBPK modelling was used to support dose recommendation in paediatric GvHD patients >28 days to 2 years where no clinical data was collected. First, a PBPK model was developed in healthy subjects and adult patients to describe DDI in the adult population. It is stated that the adult PBPK model could predict exposure within a 2-fold margin (i.e. difference between observed and simulated exposure). However, when the purpose of the PBPK predictions is to be used in exposure matching between populations the adequacy of a 2-fold prediction error is questioned. Thus, the claim that the adult PBPK model is adequate was not supported.

Several parameters in the paediatric PBPK model have been optimised during the model development which further introduces an uncertainty of the PBPK predictions. The observed paediatric PK data is fairly well described by the PBPK model, although the PK variability is under-predicted by the PBPK model.

The ontogeny of clearance pathways, anatomical and physiological changes with age are expected to be most pronounced in the age group <2 years of age. Thus, the predictive performance in age group 2-18 years does not necessarily translate to the age group <2 years. Furthermore, since no clinical data is available in the age group 28 days to <2 years, it is not possible to verify the predictions from the PBPK model.

Absorption

The new oral solution formulation has been used in a total of 21 children (F12201; n= 8 and G12201; n=13) in the paediatric studies, but no bioequivalence study has been performed comparing its bioavailability with the approved tablet. The applicant claimed that the bioavailability of the two formulations is expected to be similar, and in children between 6 and 12 years the two formulations are handled equally in the SmPC dosing instructions. Formulation is also not used as a covariate in the popPK modelling supporting the paediatric dose. Ruxolitinib has high solubility and permeability, and large differences in exposure due to formulation is not expected. Also, the MAH claimed that the excipients used in the ready to use oral solution formulation are well-established excipients in amounts that are acceptable.

Study F12201

Three formulations have been used in study F12201; tablet, capsule completely dissolved in water (not intended to be commercialized) and the proposed oral solution.

The tablet (n=9) and dissolved capsules (n=2) were used within the same age group and showed that the mean AUC_{last} and C_{max} was less than half for the capsule compared to the tablet. Since a difference in AUC between formulations would not be expected (considering the BCS class and the very rapidly dissolving tablet formulation) and since solutions compared to tablets would rather be expected to result in higher than lower C_{max}, this finding is unexpected. However, the limited number of individuals and relatively large variability suggest that these results should be interpretated with caution and no conclusions can be made.

In the ≥2y to <6y age group, both dissolved capsule (n=7) and oral solution (n=8) was administered and showed similar exposure.

In study F12201 the oral solutions and tablet was not administered within the same age group.

The median T_{max} is 1.5 h, 1.5 h and 1 h for the tablet, capsule and oral solution, respectively.

Overall discussion on BE

No formal BE studies between the different formulations have been conducted. The available PK-data for the different formulations is limited and does not include a reliable comparison between the already approved tablet and proposed oral solution. Assumptions on bioequivalence of the formulations will therefore need to rely on the fact that this is a BCS class I substance in immediate release formulations.

According to the Bioequivalence guideline and ICH M9 guideline on biopharmaceutics classification system-based biowaivers: "Applying for a BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index. The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form".

For ruxolitinib the criteria for applying for a BCS-based biowaiver is fulfilled in regard to high solubility and complete absorption (BSC class I) as well as very rapid *in vitro* dissolution for the tablet

formulation. However, the oral solution is not a solid pharmaceutical product. If strictly applying the BE-guideline, a BCS-based biowaiver is not applicable between an oral solution and a tablet. However, the oral solution has been used in the clinical studies and can therefore be considered as "clinically qualified".

Generally, for BSC class I substances and for the current case with very rapid dissolution of the tablets, the expected difference between an oral solution compared to the tablet formulation would be a similar AUC but possibly higher C_{max}. Therefore, when considering the available data as a whole, it is considered sufficiently justified that similar extent of exposure (AUC) can be expected between the new oral solution and the approved tablet. A moderately higher C_{max} when the drug is administered as an oral solution can however not be excluded, and the applicant has justified that this would not be a safety concern. Also, according to the proposed SmPC, the tablets and oral solution can be considered as interchangeable. This is acceptable.

Influence of food

No dedicated food effect studies were conducted with the two paediatric formulations (capsule and oral solution) to support this submission. A food effect study has previously been conducted with the tablet formulation and showed that the mean C_{max} was moderately decreased (24%) while the mean AUC was nearly unchanged (4% increase) when dosing with a high-fat meal.

Since no clinically relevant food effect was seen for the tablet formulation, no clinically relevant effect of food is expected for the oral solution. The oral solution may be taken with or without food which is also reflected in the SmPC.

Exposure in target population

The dosing recommendation in paediatric subjects are based on the principle of extrapolation of efficacy by matching exposure. It is agreed that Day 1 exposure should be used in the exposure matching to avoid confounding due to dose adjustments. Since only decreased dosing is allowed, the exposure given the initial dose should reflect the highest expected exposure. The target exposure in adults were defined as $AUC_{0\text{-}12h}$: 539 ng/mL. The reference range for aGvHD was defined as the 5^{th} to 95^{th} percentile adult exposure range as observed in the acute GvHD study (C2301) on Day 1. For AUC, the 5^{th} and 95^{th} percentile have a value of 121 and 1530 ng*h/mL, respectively. For Cmax, the 5^{th} and 95^{th} percentile have a value of 55.4 and 258 ng/mL, respectively. Similarly, the adult reference range for aGvHD was defined as the 5^{th} to 95th percentile adult exposure range as observed in the chronic GvHD study (D2301) on Day 1. For AUC, the 5^{th} and 95^{th} percentile have a value of 313 and 1400 ng*h/mL, respectively. For Cmax, the 5^{th} and 95^{th} percentile have a value of 67.8 and 312 ng/mL, respectively.

Population PK modelling was used to describe ruxolitinib PK in the age group 2-18 years. Subsequently, exposure metrics (primarily $AUC_{0\text{-}12h}$) based on observed data in studies F12201 and G12201 were predicted. It is apparent that subjects 2-6 years (regardless of indication) had more than halved exposure compared to the target exposure. The exposure in the age group 6-12 years was also lower than the target. The exposure is not considered similar to the target exposure and thus the dosing recommendation of 4 mg/m2 BID in paedatric subjects 2-6 years was not supported by CHMP. Following the concern of mismatched exposure between paediatric and adult GvHD patients the MAH explored alternative dosing scenarios through modelling and simulation. As recommended, the full population PK model was used to simulate doses and subsequent exposure distributions for both aGvHD and cGvHD. It is clear that the 4 mg/m2 dosing recommendation does not reach the adult reference range for cGvHD patients 2-6 years, thus the MAH proposed a revised dosing recommendation of 8 mg/m2 where 79.8% of the exposure distribution (median AUC 527 h.ng/mL) is

predicted to reach the reference exposure range (median AUC 697 h.ng/mL). This dosing recommendation was supported.

For aGvHD, 2 to 6 years, the predicted median AUC is 211 h.ng/mL, whereas the reference adult median AUC is 512 h.ng/mL. A dose of 8 mg/m2 in the aGvHD patients, 2 to 6 year, predicted a median AUC of 432 h.ng/mL which is considered a closer match with the adult reference exposure. Taking into account that there is an exposure-response relationship (identified in adults, original MAA) that could lead to lower response in the lower range of the exposure distribution, the 8 mg/m2 dose would be preferable also in the aGvHD population. In the response to questions, the MAH agreed to recommend the 8 mg/m2 dose in the aGvHD population.

No subjects were studied in the age range 28 days to <2 years. Hence, PBPK modelling was used to provide exposure predictions to support a dosing recommendation. The predicted exposures are higher than the predicted exposure based on popPK in the age range 2-6 years which was slightly concerning. Since there are no clinical data to verify the model predictions (simulations) in the age range 28 days to <2 years age, the PBPK model is not considered qualified for the prediction purpose. As an additional analysis, the MAH was asked to provide simulated exposures based on the full popPK model adapted to the relevant age group. The popPK predicted exposures in the age group <2 years are higher than the predictions given the PBPK model which is in line with the results in the older children where the initial PBPK dose predictions resulted in observed exposures lower than expected. Since there is no PK data available in patients <2 years of age where the effects of CYP ontogeny are most pronounced, some uncertainty about the dose predictions still remain. Nevertheless given that the predicted paediatric mean AUC for the proposed 8 mg/m2 dose is lower but within the reference adult range, for both indications, this provides some margin of error of the proposed doses. When applying extrapolation of efficacy based on exposure matching, and an exposure-response relationship is evident, it is desirable to aim for the central tendency of the reference exposure range. However, to mitigate the remaining uncertainty in the exposure predictions the proposed dose of 8 mg/m2 in <2 years of age is acceptable.

Exposure-response

Exposure-response analyses was provided to support the assumption that the same exposure in paediatric and adult patients give the same response. The available exposure data have several limitations. (1) Both populations are based on one dose level and the lack of several randomised doses means that confounded exposure-response relationships cannot be excluded. (2) Dose adjustments based on response are allowed during the treatment which means that the exposure cannot be considered independent of the response. (3) The time-averaged exposure introduces an uncertainty of what actual exposure gives rise to the response. Thus, the exposure-response relationships are not considered reliable and were not assessed in depth. Nevertheless, the extrapolation of efficacy from adults to paediatric patients is not questioned and the dosing recommendation in paediatric patients could be based on the principle of exposure matching (Day 1 exposure).

2.6.4. Conclusions on clinical pharmacology

The new oral solution has been used in 21 children in the paediatric studies, but no BE-study has been performed comparing its bioavailability with the approved tablet. Ruxolitinib has high solubility and permeability (BSC class I) and the applicant claims that the bioavailability of the two formulations is expected to be similar, are accepted. It is also considered sufficiently justified that similar extent of exposure (AUC) can be expected between the new oral solution and the approved tablet. A moderately higher C_{max} when the drug is administered as an oral solution can however not be excluded, and the MAH has adequately justified that this would not be a safety concern.

At the proposed (revised) posology, the paediatric exposure in aGvHD and cGvHD is considered similar to the reference (adult) exposure. Thus, the dosing recommendation in paedatric subjects is supported.

2.6.5. Clinical efficacy

2.6.5.1. Dose response studies

See PK assessment.

2.6.5.2. Main studies

To support efficacy claims, efficacy data is reported from:

- two open-label, single arm studies in paediatric subjects (Study F12201 and G12201), and
- additional analyses performed on data pooled from Study F12201 and adolescents randomized to ruxolitinib treatment in Study C2301 for acute GvHD, and on data pooled from Study G12201 and adolescents randomized to ruxolitinib treatment in Study D2301 for chronic GvHD.

The randomized studies C2301 and D2301 were previously evaluated to obtain approval in acute or chronic GvHD in adults and adolescents in the EU.

Table 14 Overview of studies included in paediatric pool and their status

Study no./design/study population	LPLV/ Data cut-off date Study status	Duration of treatment and follow-up	Dose	No of subjects treated with Rux
Acute GvHD				
Paediatric study: Study F12201 (REACH 4) A Phase I/II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in paediatric subjects with Grade II-IV SR-acute GvHD or treatment-naïve acute GvHD after alloHSCT.	02-Feb-2023 (Final analysis) Study completed	Treatment period: Day 1 to Week 24 / EOT Safety follow-up period: Last dose + 30 days Long-term follow-up period: From EOT to Month 24 (follow-up at months 12, 18, 24)	**Group 1** ≥ 12 y to < 18 y 10 mg b.i.d. (N=18) **Group 2** ≥ 6 y to < 12 y 5 mg b.i.d. (N=12) **Group 3** ≥ 2 y to < 6 y 4 mg/m2 b.i.d. (N=15) **Group 4** ≥ 28 days to < 2 y (NA)	45
Study providing additional data: *Study C2301 (REACH 2)* A randomized Phase III open-label multicenter study of ruxolitinib compared to Investigator choice best available therapy (BAT) in alloHSCT recipients, adults and adolescents ≥ 12 years old, with Grade II-IV SR-acute GvHD. Randomization for ruxolitinib vs. BAT = 1:1	23-Apr-2021 (Final analysis) Study completed	Treatment period: Day 1 to Week 24 / EOT Safety follow-up period: Last dose + 30 days Long-term follow-up period: From EOT to Month 24 (follow-up at months 6, 9, 12, 18, 24)	**Ruxolitinib**: 10 mg b.i.d. **BAT**: varied depending upon Investigator's choice identified prior to randomization. Dose and frequency depended on label (where approved) and institutional guidelines for various BAT.	5 paediatric subjects[1] (aged ≥ 12 to <18 y) were randomized to Rux
Chronic GVHD				

Study no./design/study population	LPLV/ Data cut-off date Study status	Duration of treatment and follow-up	Dose	No of subjects treated with Rux
Paediatric study: ***Study G12201 (REACH 5)*** A Phase II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in paediatric subjects with moderate or severe SR-chronic GvHD or treatment-naïve chronic GvHD after alloHSCT	19-Oct-2022 (Interim analysis) Study ongoing	Treatment period: Cycle 1 Day 1 up to 3 years (39 cycles/156 weeks) Safety follow-up period: Last dose + 30 days Long-term follow-up period: after EOT every 6 months until 3 years (calculated from first dose)	**Group 1** ≥ 12 y to < 18 y 10 mg b.i.d. (N=22) **Group 2** ≥ 6 y to < 12 y 5 mg b.i.d. (N=16) **Group 3** ≥ 2 y to < 6 y 4 mg/m2 b.i.d. (N=7) **Group 4** ≥ 28 days to < 2 y (NA)	46 [3]
Study providing additional data: ***Study D2301 (REACH 3)*** A randomized Phase III open-label multicenter study of ruxolitinib vs. BAT (1:1 randomization) in adults and adolescent subjects (≥12 to <18 years old) with moderate or severe corticosteroid-refractory chronic GvHD after alloHSCT.	15-Dec-2022 (Final analysis) Study completed	Treatment period: Cycle 1 Day 1 till Cycle 6 Day 28 (subjects could continue into the extension period: Cycle 7 to Cycle 39) Safety follow-up period: Last dose + 30 days Long-term survival follow-up period: Every 3 months from EOT until the completion of 39 cycles	**Ruxolitinib**: 10 mg b.i.d. **BAT**: varied depending upon Investigator's choice identified prior to randomization. Dose and frequency depended on label (where approved) and institutional guidelines for various BAT.	4 adolescent subjects[2] (aged ≥ 12 to <18 y) were randomized to Rux

[1]: Study C2301: 5 paediatric subjects were randomized to the Rux arm. One paediatric subject who crossed over to ruxolitinib from the BAT arm is not part of the pooled efficacy analyses but is part of the safety analyses [INC424F1/G1 SCS].

[2]: Study D2301: 4 paediatric subjects were randomized to the ruxolitinib arm; 6 paediatric subjects who crossed over to ruxolitinib from the BAT arm are not part of the pooled efficacy analyses but are part of the safety analyses [INC424F1/G1 SCS].

Rux=ruxolitinib; BAT=best available therapy; SR = corticosteroid refractory

NA: Group 4 in Study F12201 and Study G12201 was not open for subject recruitment. Efficacy extrapolation was performed for this age group.

Source: [Study F12201 Final CSR], [Study G12201 Primary analysis CSR], [Study C2301 Final CSR], [Study D2301 Final CSR]

Study F12201 (REACH4) in acute GvHD: Phase I/II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in paediatric subjects with grade II-IV acute GvHD after alloHSCT

The purpose of the study was to assess safety, efficacy, and pharmacokinetics of ruxolitinib treatment with corticosteroids in treatment-naïve and SR aGvHD subjects aged ≥ 28 days to <18 years of age.

Methods

- **Study Participants**

Key inclusion criteria

- Age ≥ 28 days and < 18 years

- Undergone alloHSCT from any donor source using bone marrow, peripheral blood stem cells, or cord blood. Recipients of myeloablative or reduced intensity conditioning are eligible.
- Grades II-IV acute GvHD within 48 hours prior to study treatment start, either:
    - Treatment-naïve Grades II-IV acute GvHD as per Harris et al 2016, or
    - Steroid refractory Grades II-IV acute GvHD following allogeneic HSCT as per institutional criteria, or per physician decision in case institutional criteria are not available, and the subject is currently receiving systemic corticosteroids.

Key exclusion criteria

- Received the following systemic therapy for acute GvHD:
    - Treatment-naïve acute GvHD subjects having 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
    - SR-acute GvHD subjects having received two or more prior systemic treatment for acute GvHD in addition to corticosteroids.
- Any corticosteroid therapy for indications other than acute GvHD at doses > 1 mg/kg/day methylprednisolone within 7 days of Screening.
- Subjects who received JAK inhibitor for any indication after initiation of alloHSCT conditioning.

Although inclusion of subjects aged 28 days to <2 years was planned in study F12201, no subjects in this age range were enrolled, as the total sample size of 45 subjects was enrolled before availability of the PK data to select the dose and allow enrollment into Group 4 (28 days to <2 years).

- **Treatments**

Ruxolitinib treatment

Subjects received ruxolitinib twice a day for a planned duration of 24 weeks, see dosing in table below.

Table 1 Dosing of ruxolitinib in study F12201

Table 6-1 Dose and treatment schedule

Study treatments	Age groups	Pharmaceutical form and Route of Administration	Starting dose	Frequency and/or Regimen
Ruxolitinib (INC424)	Group 1	5-mg tablet for oral use OR oral pediatric formulation for oral or NG use *	10 mg BID (2 tablets BID) OR 10 mg BID oral pediatric formulation**	Twice per day
Ruxolitinib (INC424)	Group 2	5-mg tablet for oral use OR oral pediatric formulation for oral or NG use*	5 mg BID (1 tablet BID) OR 5 mg BID oral pediatric formulation**	Twice per day
Ruxolitinib (INC424)	Group 3	5-mg tablet for oral use OR oral pediatric formulation for oral or NG use*	4 mg/m^2 BID (either tablet OR oral pediatric formulation)**	Twice per day
Ruxolitinib (INC424)	Group 4	5-mg tablet for oral use OR oral pediatric formulation for oral or NG use*	To be defined	Twice per day

*Tablet for oral use may be crushed as per instructions in the pharmacy manual (if calculated dose based on BSA is not 5 mg or 10 mg, then crushing is not permitted). Tablet cannot be broken to achieve partial doses. In this case, oral pediatric formulation should be administered (taken in liquid form). Oral pediatric formulation should be dispensed according to instructions in the pharmacy manual. Refer to the pharmacy manual for nasogastric tube administration details.
Note: Crushed tablet cannot be administered via nasogastric (NG) tube.
**BSA- based calculated doses should be administered as per instructions in the pharmacy manual.

Group 1 ≥ 12 y to < 18 y, Group 2 ≥ 6 y to < 12 y, Group 3 ≥ 2 y to < 6, Group 4 ≥ 28 d to < 2 y.

Concomitant treatment

In addition to ruxolitinib, the following concomitant non-investigational treatment with systemic corticosteroids +/- CNI was required as per standard of care:

- **Treatment naïve acute GvHD:** in addition to ruxolitinib, treatment must include methylprednisolone (or equivalent prednisone) +/- cyclosporine or tacrolimus at standard dosing adjusted to therapeutic trough levels.
- **SR-acute GvHD:** in addition to ruxolitinib, concomitant use of corticosteroids +/- cyclosporine or tacrolimus at standard dosing adjusted to therapeutic trough levels.

Other systemic medications used for prophylaxis of aGvHD could be continued after Day 1 only if started prior to diagnosis of aGvHD.

Tapering of ruxolitinib and concomitant immunosuppression

Tapering of immunosuppression should follow these steps according to the protocol version 3:

1. **Corticosteroids:** the taper of corticosteroids in patients demonstrating a PR or CR as observed by the Investigator must not be initiated earlier than Day 7, and should be performed per institutional guidelines (e.g. 10% dose reduction every 5 days, and continuing to approximately Day 56 to allow 7-8 week taper).
2. **CNI (cyclosporine or tacrolimus):** CNI taper is allowed in patients demonstrating a PR or CR, once off corticosteroids, and should then be performed per institutional guidelines (e.g. 25% dose reduction per month).
3. **Ruxolitinib:** ruxolitinib taper is allowed in patients demonstrating a PR or CR, once off corticosteroids, and must not start earlier than Day 56. If applicable, the taper of CNI and

ruxolitinib may be performed at the same time. The protocol guidance for ruxolitinib tapering is a 50% dose reduction every 2 months based on the clinical judgment of the Investigator.

All patients must be off corticosteroids, CNIs and ruxolitinib by the Week 48 maximum.

Discontinuation of ruxolitinib

Ruxolitinib treatment was required to be discontinued under any of the following circumstances:

- Lack of response to acute GvHD treatment at Day 28
- Subjects requiring new systemic therapy for acute GvHD at any time
- Acute GvHD flare occurring during ruxolitinib taper after Week 24
- Development of signs or symptoms of chronic GvHD including de novo or overlap
- Underlying hematological disease progression or relapse
- Evidence of graft failure necessitating rapid taper of immunosuppression, administration of non-scheduled DLI, stem cell boost, chemotherapy, or other treatment that would expectedly affect acute GvHD
- The Investigator believe that continuation would be detrimental to the subject's well-being
- Subject had not weaned off corticosteroids, CNIs and ruxolitinib by Week 48

- **Objectives and outcomes/endpoints**

Primary objectives/endpoints

Table 2 Primary objectives and endpoints in Phase 1 and 2 of study F12201, respectively

Table 8-1 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.

In study F12201, it was not planned to test specific efficacy hypotheses, but to provide estimates of efficacy endpoints for the paediatric study population. Summary statistics (frequencies and percentages) was to be provided.

Organ staging of aGvHD was performed according to updated NIH criteria as described by Harris et al 2016.

aGvHD assessments was performed by the treating team according to standard criteria (Harris et al 2016) with regard to skin; liver; upper GI; lower GI and overall grading on a weekly basis for the first 8 weeks and then every 28 days thereafter during the treatment period and at EOT visit.

Table 3 Response assessment of aGvHD in study F12201

Table 8-3 Response assessment

Efficacy assessments:

aGvHD response assessment will be made with respect to the organ stage at screening and Day 1:

4. **Complete response** is defined as a score of 0 for the aGvHD grading in all evaluable organs that indicates complete resolution of all signs and symptoms of aGvHD in all evaluable organs without administration of additional systemic therapy for any earlier progression, mixed response or non-response of aGvHD.
5. **Partial response** is defined as improvement of 1 stage in 1 or more organs involved with aGvHD signs or symptoms without progression in other organs or sites without administration of additional systemic therapy for an earlier progression, mixed response or non-response of aGvHD.
6. **Lack of response** is defined as no response, mixed response, or progression.
7. **No response** is defined as absence of improvement in any organ involved by aGvHD, without worsening in any involved organ.
8. **Mixed response** is defined as improvement of at least 1 stage in the severity of aGvHD in one organ accompanied by progression in another organ or development of signs or symptoms of aGvHD in a new organ.
9. **Progression** is defined as worsening in 1 or more organs by 1 or more stages without improvement in any involved organ.

Patients requiring additional systemic therapy for aGvHD will be classified as non-responders.

aGvHD Flare is defined as any increase in signs or symptoms of aGvHD that is sustained for >24h after an initial response (CR or PR) and requires re-escalation of immunosuppressive therapy (e.g. corticosteroid, CNI and/or ruxolitinib dosing). While all aGvHD flares will be captured on study whether occurring during steroid, CNI, or ruxolitinib taper, only flares that fulfill either one the following criteria will be considered a failure of treatment:

1. Addition of new systemic therapy for aGvHD due to inability to taper corticosteroids below methylprednisolone 0.5 mg/kg/day (or equivalent <0.6 mg/kg/day of prednisone) for a minimum 7 days,

OR

2. Addition of new systemic therapy for aGvHD due to re-escalation of corticosteroids to methylprednisolone >2 mg/kg/day (or equivalent >2.5 mg/kg/day of prednisone).

aGvHD assessments will be performed by the treating team according to standard criteria (Harris et al 2016) as described in Table 8-3. Disease assessments must continue per the schedule of visits weekly until Day 56, unless withdrawal of consent/ Opposition to use data/biological samples or death occurs, even in patients who are withdrawn from treatment unless consent for these assessments is specifically withdrawn.

The use of MAGIC criteria (Harris et al 2016) for staging in aGvHD is recommended according to the *EBMT–NIH–CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment* by Schoemans et al 2018.

The estimand framework was not used in this trial.

Secondary objectives/endpoints

The main secondary objective was to estimate the proportions of all patients who achieve a CR or PR at Day 28 and maintain a CR or PR at Day 56. A patient will not be considered a durable responder at Day 56 if any of the following events occurs prior to or at Day 56: (i) No CR or PR at Day 28 or at Day 56, or (ii) GvHD progression or additional systemic therapy for aGvHD.

Other secondary endpoints included incidence of malignancy relapse/progression and OS.

- **Sample size**

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 enrolment 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%.

- **Randomisation and Blinding (masking)**

N/A

- **Statistical methods**

Analysis sets

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 **Efficacy Evaluable Set (EES)** comprised all subjects to whom study treatment was assigned at the RP2D of ruxolitinib and who received at least one dose of study treatment at that dose level. In Protocol Amendment 1 (dated 1-Apr-2019), a statement was added saying that if the starting dose was different from the RP2D due to co-administration of ruxolitinib with strong CYP3A4/CYP2C9 inhibitors, these subjects would be included in the EES. In Protocol Amendment 3 (dated 24-Jun-2022), this statement was broadened to include co-administration of strong CYP3A4 inhibitors too.

In the event that subjects were treated with a starting dose that was eventually confirmed as RP2D, the Efficacy Evaluable Set was the same as the Full Analysis Set. In Protocol Amendment 3 (dated 24-Jun-2022), a statement was added that if the starting dose was different from the assigned dose level due to co-administration of ruxolitinib with strong CYP3A4 inhibitors or dual CYP3A4/CYP2C9 inhibitors, these patients were included under the assigned dose level and considered that they had received the full assigned dose. This applied to all analysis sets.

Analysis of the primary endpoints

The response rate for ORR at Day 28 was estimated on the EES. 90% confidence intervals were calculated based on the exact method for binominal distribution. Subjects with missing assessments that prevented the evaluation of the ORR were considered non-responders. This included acute GvHD response assessments at baseline and Days 28, 56. Subjects who discontinued the study treatment prior to the completion of the Day 28 visit were considered non-responders.

The following analysis windows were applied to the target day for assessments on overall response, where target day for Week X is X*7:

Baseline assessment was the last acute GvHD assessment prior to or at the start of study treatment (Day 1).

Weeks 1, 2, 3, 4, 5, 6, 7, 8: -3 days/+3 days

Weeks 12 to 48: -13 days/+14 days

Analysis of the secondary endpoints

All secondary efficacy endpoints were analysed using the EES.

Durable ORR at Day 56 (the key secondary endpoint) was estimated with 90% confidence intervals calculated based on the exact method for binominal distribution.

Duration of response was summarized for all subjects in the EES with overall response of CR or PR at Day 28. Cumulative incidence rates and 95% CIs at 1, 2, 6, 12, 18 and 24 months were presented. The cumulative incidence curve was plotted. Death without prior observation of acute GvHD

progression and onset of chronic GvHD were considered to be competing risks. Subjects were censored at the last response assessment prior to or at the analysis cut-off date, if no events/competing risk occurred on or before 4 weeks (28 days) after the last GvHD assessment.

The weekly cumulative steroid dose was calculated for each subject up to Day 56 and the overall cumulative steroid dose was calculated for each subject at Day 56. As specified in the statistical analysis plan (but not in the protocol), the proportion of subjects with any dose reduction and any dose reduction of at least 50% in corticosteroids from baseline until EOT was also provided. Doses of methylprednisolone were converted to prednisone equivalents by multiplying the methylprednisolone dose by 1.25. In addition, the RDI, by week, was calculated relative to the starting dose of corticosteroids and categorized as (1) complete reduction where subjects are tapered off corticosteroids by Day 56, (2) ≤50% RDI and (3) >50% RDI. The proportion of subjects in each category and corresponding 95% Cis were presented.

Additionally, the proportion of subjects with any dose or 50% reduction of corticosteroids dose until Day 56 from baseline have been also provided. The proportion of subjects in each category and corresponding 95% confidence intervals were presented by treatment group.

Error probabilities, adjustment for multiplicity and interim analyses

No hypothesis tests were performed in this study, but 90% confidence intervals were calculated.

No formal interim analysis was planned for this study. However, summaries of safety and PK data were produced to support the regular safety monitoring conducted by the DMC and the confirmation of RP2D.

Changes from protocol-specified analyses

After approval of the Statistical Analysis Plan (SAP) amendment 3 and after Data Base Lock happened on 16-Mar-2023, a misspecification in the censoring rule used for the duration of response analysis has been identified that can lead to potential overestimation of the duration of response. With the underlined text in the below definition, the censoring rule was further specified to ensure that the period when events and competing risks are considered corresponds to the period when those events and competing risks were collected in the database, to not presume that a patient was still in response beyond last GvHD response assessment or collection of new systemic therapy. This updated definition was used for the CSR analyses. No change in the output shells were required.

Duration of Response

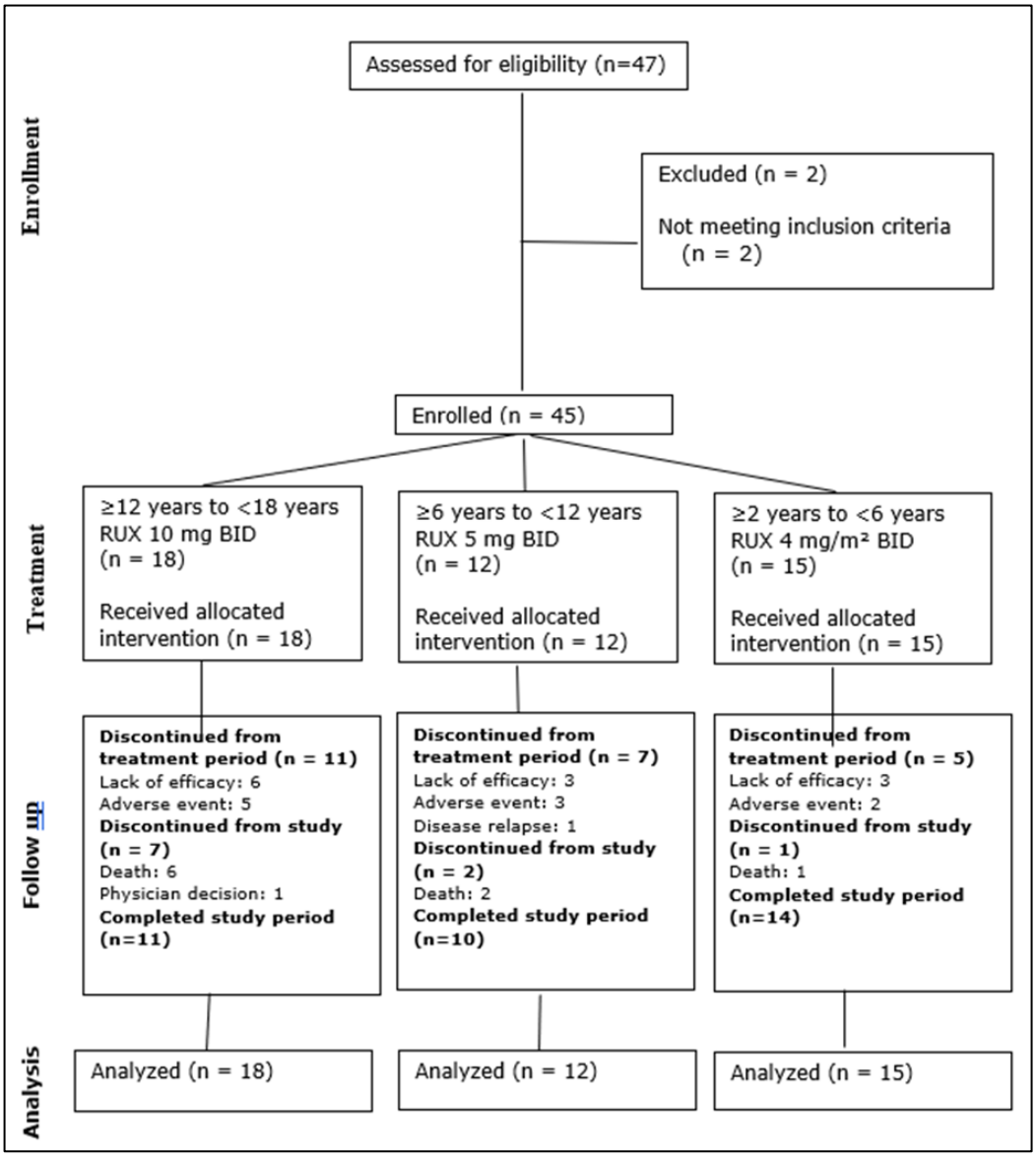
Duration of response was calculated for patients whose overall response at Day 28 was CR or PR according to updated standard criteria (Harris et al 2016). The start date was the date of first documented response of CR or PR (i.e., the start date of response), which could be prior to or at Day 28. If it was prior to Day 28, there should not be progression or addition of systemic therapies for aGvHD between the start date of response and Day 28. The end date was defined as the date of progression or the date of addition of systemic therapies for aGvHD on or after Day28, since this constituted a non-response. The date of progression was the earliest date of PD recorded in the aGvHD assessment CRF page or the date of death due to aGvHD in the death CRF page.

Death without prior observation of aGvHD progression (i.e. date of death due to non aGVHD reason (Other) in the death CRF page) and onset of chronic GvHD are considered to be competing risks.

Duration of response will be censored at the last response assessment prior to or at the analysis cut-off date, if no events/competing risks occurred on or before 4 weeks (28 days) after the last GvHD assessment (4 weeks for acute GvHD because frequency of GvHD assessment was planned every 4 weeks after Day 56).

Results

- **Participant flow**



- **Recruitment**

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

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

Data cut-off date: 02-Feb-2023, final analysis, Final CSR

- **Conduct of the study**

Protocol amendments

The original study protocol was dated 02-Mar-2018 and was amended 3 times, see key features of each amendment in table below.

Table 19 Key features of protocol amendments in study F12201

Version and date	Summary of key changes
Amendment 1 (01-Apr-2019)	The main purpose of this amendment was to broaden the eligible subject populations, modify study assessment and revise safety dose modifications based on feedback from investigators on current practices in the management of acute GvHD. The number of subjects was expanded to a total of 45 subjects treated at the RP2D, thus increasing the number of subjects for safety and efficacy evaluation.
Amendment 2 (14-Oct-2020)	The main purpose of amendment 2 was to update the guidelines regarding the management of ruxolitinib based on liver monitoring laboratory results, to update the inclusion criteria to allow for nasogastric tube administration of the pediatric formulation, to provide clarifications regarding the management of ruxolitinib tapering, to update contraception guidelines and pregnancy reporting requirements for female subjects of child-bearing potential and to clarify requirements for ruxolitinib post-trial access. The assessment of benefit and risk related to SARS-CoV-2 virus and the COVID-19 pandemic determined no substantial additional risk for subject safety at this time.
Amendment 3 (24-Jun-2022)	The main purpose of this amendment to include public health emergency disruption proofing language, to provide guidance on subject management, including withdrawal of consent, and to decrease the minimum enrollment requirements of treatment-naïve subjects from 40% to at least 20% due to recruitment challenges. The sample remains representative of the study population and therefore the sample size was not re-estimated due to this modification.

- **Baseline data**

Table 20 Pre-transplant Disease history in study F12201

Table 10-5 Disease History (Full Analysis Set)

Characteristic Categories/Statistics	≥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 (%)
Primary diagnosis classification-n (%)				
Malignant-leukemia/MDS	12 (66.7)	9 (75.0)	5 (33.3)	26 (57.8)
Malignant-lymphoproliferative	0	1 (8.3)	0	1 (2.2)
Non-malignant-severe aplastic anemia	2 (11.1)	2 (16.7)	3 (20.0)	7 (15.6)
Other	4 (22.2)	0	7 (46.7)	11 (24.4)
Diagnosis of underlying Malignant disease-n (%)				
Acute lymphoblastic leukemia (ALL)	6 (33.3)	7 (58.3)	2 (13.3)	15 (33.3)
Acute myelogenous leukemia (AML)	2 (11.1)	2 (16.7)	2 (13.3)	6 (13.3)
Chronic myelogenous leukemia (CML)	1 (5.6)	0	0	1 (2.2)
Myelodysplastic disorder (MDS)	2 (11.1)	0	0	2 (4.4)
Non-hodgkin lymphoma	0	1 (8.3)	0	1 (2.2)
Other leukemia	0	0	1 (6.7)	1 (2.2)
Other	1 (5.6)	0	0	1 (2.2)
Diagnosis of underlying non-Malignant disease-n (%)				
Autoimmune diseases	1 (5.6)	0	0	1 (2.2)
Disorders of the immune system	2 (11.1)	0	3 (20.0)	5 (11.1)
Histiocytic disorders	1 (5.6)	0	2 (13.3)	3 (6.7)
Severe aplastic anemia	2 (11.1)	2 (16.7)	3 (20.0)	7 (15.6)
Other	0	0	2 (13.3)	2 (4.4)
Diagnosis of underlying other specify-n (%)				
Blastic plasmacytoid dendritic cell neoplasm	1 (5.6)	0	0	1 (2.2)
Chronic granulomatosis disease	1 (5.6)	0	0	1 (2.2)
Emberger syndroma, subject and his family with gata 2 mutation	0	0	1 (6.7)	1 (2.2)
Immune deficiency.	1 (5.6)	0	0	1 (2.2)
UNC 13 defficiency, generalised infection with the rubella-virus vaccination	0	0	1 (6.7)	1 (2.2)
Missing	15 (83.3)	12 (100)	13 (86.7)	40 (88.9)
Time from diagnosis of underlying disease to screening (weeks)				
n	18	12	15	45
Mean (SD)	203.8 (262.8)	137.7 (75.28)	53.8 (31.05)	136.1 (180.6)
Median	63.9	143.6	43.9	65.3
Min-Max	14.1 - 801.0	21.9 - 287.9	23.1 - 130.7	14.1 - 801.0
Time from diagnosis of underlying disease to transplant (weeks)				
n	18	12	15	45
Mean (SD)	192.3 (263.1)	132.0 (75.83)	43.0 (22.78)	126.5 (180.3)
Median	45.4	139.6	37.9	55.3
Min-Max	10.9 - 796.9	17.9 - 282.6	10.7 - 89.0	10.7 - 796.9
CIBMTR risk assessment-n (%)				
Low	2 (11.1)	2 (16.7)	6 (40.0)	10 (22.2)
Intermediate	4 (22.2)	3 (25.0)	2 (13.3)	9 (20.0)
High	4 (22.2)	2 (16.7)	3 (20.0)	9 (20.0)
Unknown	6 (33.3)	4 (33.3)	2 (13.3)	12 (26.7)
Missing	2 (11.1)	1 (8.3)	2 (13.3)	5 (11.1)

CIBMTR = Center for International Blood and Marrow Transplant Research
Analyses of 'time from ... to ...' are given only for subjects with all dates available.

Thirty two subjects (71%) had steroid-refractory acute GvHD with the remaining 13 subjects (29%) being treatment-naïve.

The majority had Grade II aGvHD at the start of study treatment (64%, n=29), while 27% (n= 12) had grade III and 9% (n=4) hade grade IV.

The majority of subjects (76%) had skin involvement, followed by lower GI involvement in 40% of subjects at baseline. The skin, liver, or GI involvement could be combined with other organ involvements in the same subject.

The most frequent conditioning regimen was Myeloablative, reported in 34 subjects (76%), followed by Reduced intensity in 7 subjects (16%) and Non-myeloablative in 3 subjects (7%). Reduced intensity and Non-myeloablative conditioning regimens were more often used in the youngest studied age group > 2 to < 6 years.

Overall, the stem cell source was bone marrow in 60% (n=27) of the subjects, and peripheral blood in 33% (n=15) of the subjects, and single cord blood in 7% (n=3). Stem cell source was in general similar between the different age groups.

The median donor age was 31 years (range 5-58) and overall similar between the different age groups.

In principle, the study population reflects the intended indication although the sample size is limited and there is heterogeneity in multiple parameters such as age, disease history, transplant-related history, prior and concomitant medication.

Prior therapy

Thirty-nine subjects (87%) received prior **aGvHD prophylaxis** which started and ended prior to study treatment start date. The most frequent therapies for aGvHD prophylaxis were ciclosporin (19 subjects, 42%), tacrolimus, (10 subjects, 22%), methotrexate (9 subjects, 20%).

Forty-two subjects (94%) received **systemic corticosteroid** prior to starting treatment with a median exposure of 14 days with minimum 1 day and maximum 457 days. The median corticosteroid dose at start of study treatment was 2 mg/kg/day (Min-Max: 0.1 – 5.1). Of note, Treatment naïve subjects could receive up to a maximum of 72h of prior systemic corticosteroid therapy of methylprednisolone or equivalent after the onset of acute GvHD.

Overall, 19 subjects (42%) had prior treatment and/or prophylaxis with corticosteroid + CNI + other systemic treatment, and 17 subjects (38%) had prior or corticosteroid + CNI.

Concomitant therapy

In study F12201, concomitant non-investigational treatment with systemic corticosteroids +/- CNI was required as per standard of care in addition to ruxolitinib treatment in study F12201.

At Baseline, all subjects received **systemic corticosteroids**. Average daily steroid dosing is presented in figure below.

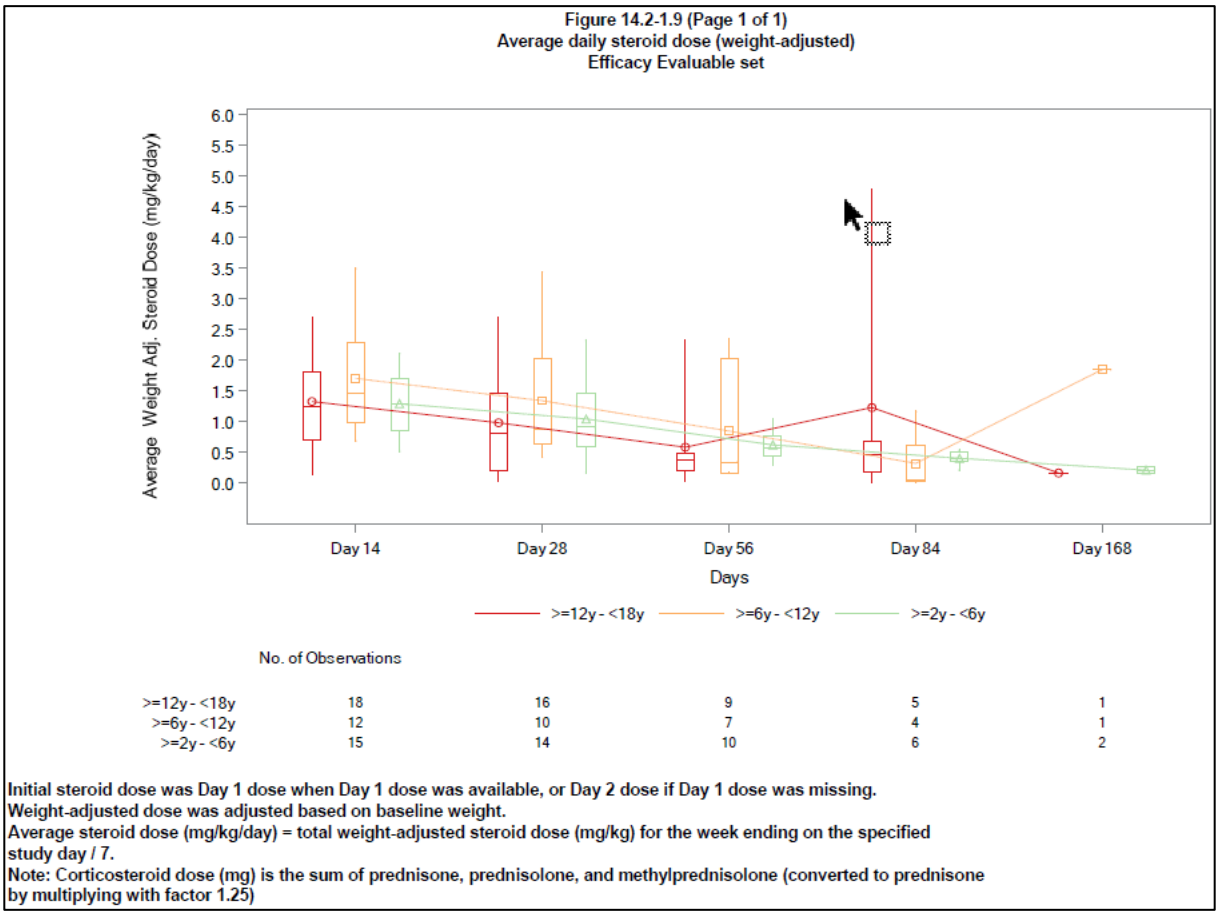


Figure 2 Average daily steroid dose in study F12201

In addition to concomitant steroid treatment, 40 subjects (88.9%) received concomitant **CNIs**.

Moreover, the MAH states that 12 subjects (27%) had **additional systemic aGvHD therapy** after the start of the study treatment including 3 subjects (7%) who had interleukin inhibitors and 7 subjects (16%) who had selective immunosuppressants such as mycophenolate mofetil, abatacept, ATG and sirolimus.

In addition, the MAH reports that 12 subjects (27%) received **aGvHD prophylaxis** medication on or after the study treatment start date.

With regard to concomitant use of **CYP3A inhibitors**, 32 subjects (71%) used concomitant CYP3A4 inhibitors, most commonly posaconazole. According to the protocol, ruxolitinib dose may be reduced by 50% upon initiation of a strong CYP3A4 inhibitor or a dual CYP3A4/CYP2C9 inhibitor, and, in Protocol Amendment 3 a statement was added that if the starting dose of ruxolitinib was different from the assigned dose level due to co-administration with strong CYP3A4 inhibitors or dual CYP3A4/CYP2C9 inhibitors, these patients were included under the assigned dose level and considered that they had received the full assigned dose.

Exposure

Median exposure time to **ruxolitinib** in study F12201 was 117 days, with a minimum of 8.0 days and a maximum of 342.0 days. More than half of the subjects (58%, 26 subjects) received ruxolitinib for >112 days (4 months). Median exposure was longer in SR-GvHD subjects (128 days) than in treatment-naïve subjects (111 days).

Duration of exposure to **corticosteroids** was <= 28 days for 5 subjects (11%), > 28 – 56 days for 16 subjects (36%), > 56 – 112 days for 16 subjects (36%), > 112 – 168 days for 3 subjects (7%), > 168 – 336 days for 4 subjects (9%) and > 336 – 672 days for 1 subject (2%).

Median exposure to **CNIs** was highest in the ≥ 2 y to < 6 y age group (146 days, min: 1, max: 317), followed by the ≥ 6 y to < 12 y age group (106 days, min: 20, max: 193) and the ≥ 12 y to < 18 y age group (100 days, min: 8, max: 365).

- **Numbers analysed**

Table 21 Analysis sets in study F12201

Analysis 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 (%)
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)

- **Outcomes and estimation**

The final analysis of study F12201 (Final CSR, data cut-off date 02-Feb-2023) took place once all subjects had completed the Long-Term Follow-Up period, i.e. reached Month 24, unless the subject discontinued earlier.

Primary efficacy evaluation was based on the Efficacy Evaluable Set which included all subjects to whom study treatment was assigned at the RP2D of ruxolitinib and who received at least one dose of study treatment at that dose level. All subjects in this study were treated based on the assigned dose level that was confirmed as the RP2D of each age group. Therefore, the Efficacy Evaluable Set was the same as the Full analysis Set.

In the current submission, efficacy evaluations in paediatric subjects with aGvHD were based on the pooled data from the

i. Paediatric Study F12201 (REACH 4, N=45), and from

ii. Adolescent subjects treated with ruxolitinib treatment in Study C2301 (REACH 2, N=5)

Primary endpoint – ORR at day 28

Table 4 ORR at day 28 in the Pooled acute GvHD paediatric subjects study F12201 + C2301 (Full analysis set)

	Study F12201				Study C2301	Studies F12201+C2301
	≥12y - <18y 10mg b.i.d.	≥6y - <12y 5mg b.i.d.	≥2y - <6y 4mg/m² b.i.d.	All subjects	≥12y - <18y 10mg b.i.d.	Total pediatric subjects
	N=18 n (%)	N=12 n (%)	N=15 n (%)	N=45 n (%)	N=5 n (%)	N=50 n (%)
Overall response						
Responders						
Complete Response (CR)	8 (44.4)	4 (33.3)	10 (66.7)	22 (48.9)	3 (60.0)	25 (50.0)
Partial Response (PR)	7 (38.9)	6 (50.0)	3 (20.0)	16 (35.6)	1 (20.0)	17 (34.0)
Non-responders						
No response	1 (5.6)	0	1 (6.7)	2 (4.4)	0	2 (4.0)
Mixed response	0	0	0	0	0	0
Progression	0	0	1 (6.7)	1 (2.2)	0	1 (2.0)
Other *	0	0	0	0	0	0
Unknown	2 (11.1)	2 (16.7)	0	4 (8.9)	1 (20.0)	5 (10.0)
Death	0	0	0	0	0	0
Early discontinuation	2 (11.1)	2 (16.7)	0	4 (8.9)	1 (20.0)	5 (10.0)
Missing visits	0	0	0	0	0	0
Overall Response Rate (ORR: CR+PR)	15 (83.3)	10 (83.3)	13 (86.7)	38 (84.4)	4 (80.0)	42 (84.0)
90% CI for ORR	(62.3, 95.3)	(56.2, 97.0)	(63.7, 97.6)	(72.8, 92.5)	(34.3, 99.0)	(73.0, 91.8)

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

It is noted that the MAH use 90% CI for the efficacy results in the SmPC section 5.1.

ORR at day 28 was 69% (90% CI: 43, 89) in Treatment-naïve subjects, and 91% (90% CI: 78, 97) in SR-refractory patients in study F12201. The MAH argues that this difference may be attributed to baseline organ involvement and organ stage, pre-transplant disease history and early discontinuation rate among subjects with Treatment-naïve or SR aGvHD.

Subgroup analysis of ORR at day 28 in the Pooled aGvHD paediatric subjects by severity (GvHD grade at baseline) showed no clear trend for ORR, although the analyses is limited by small number of subjects with grade III or grade IV.

The ORR at Day 28 showed consistency (>80%) across the age groups in Study F12201. The CR at day 28 was numerically higher in the age group >2 to < 6 years (67%) vs 33% in age group >6 to <12 years and 44% in age group >6 to < 12 years.

Selected secondary endpoints

Durable ORR at Day 56 (key secondary endpoint) 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. See table below.

Table 5 Durable ORR at day 56 in the Pooled aGvHD paediatric subjects study F12201 + C2301(Full analysis set)

	Study F12201				Study C2301	Studies F12201+C2301
	≥12y - <18y 10mg b.i.d. N=18 n (%)	≥6y - <12y 5mg b.i.d. N=12 n (%)	≥2y - <6y 4mg/m² b.i.d. N=15 n (%)	All subjects N=45 n (%)	≥12y - <18y 10mg b.i.d. N=5 n (%)	Total pediatric subjects N=50 n (%)
Overall response						
Responders						
Complete Response (CR)	7 (38.9)	6 (50.0)	9 (60.0)	22 (48.9)	3 (60.0)	25 (50.0)
Partial Response (PR)	3 (16.7)	3 (25.0)	2 (13.3)	8 (17.8)	1 (20.0)	9 (18.0)
Non-responders						
No response	1 (5.6)	0	0	1 (2.2)	0	1 (2.0)
Mixed response	1 (5.6)	0	1 (6.7)	2 (4.4)	0	2 (4.0)
Progression	0	0	0	0	0	0
Other *	0	0	0	0	0	0
Unknown	3 (16.7)	1 (8.3)	1 (6.7)	5 (11.1)	0	5 (10.0)
Death	0	0	0	0	0	0
Early discontinuation	3 (16.7)	1 (8.3)	1 (6.7)	5 (11.1)	0	5 (10.0)
Missing visits	0	0	0	0	0	0
Overall Response Rate (ORR: CR+PR)	10 (55.6)	9 (75.0)	11 (73.3)	30 (66.7)	4 (80.0)	34 (68.0)
90% CI for ORR	(34.1,75.6)	(47.3,92.8)	(48.9,90.3)	(53.4,78.2)	(34.3,99.0)	(55.5,78.8)

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

In the SR-aGvHD group, 22 subjects (69%) demonstrated durable ORR at Day 56, 15 (47%) reporting CR. In the Treatment-naive group, 8 subjects (62%) demonstrated durable ORR at Day 56, 7 (54%) reporting CR.

The **OS** analysis was performed using follow-up data from the pooled paediatric data in aGvHD, including 12 (24%) deaths and 38 (76%) subjects alive by the end of the study. Kaplan-Meier estimated median OS was not reached.

Regarding **Malignancy Relapse/Progression**, a total of 30 subjects with underlying malignant hematological disease were included in the Pooled aGvHD paediatric subject analysis, of whom, malignancy relapse/progression was reported in 6 (20%) subjects and competing risk of non-malignancy relapse/progression deaths was reported in 4 (13%) subjects.

Regarding **tapering of corticosteroids** in study F12201, 4 subjects (9%) had completely tapered off corticosteroids and 39 subjects (87%) had some dose reduction by Day 28. Seventeen subjects (38%) had completely tapered off corticosteroids and 42 subjects (93%) had any dose reduction by Day 56 with 34 subjects (76%) reporting a reduction greater than 50%. Twenty eight subjects (62%) had completely tapered off corticosteroids and 43 subjects (96%) had any dose reduction by EOT.

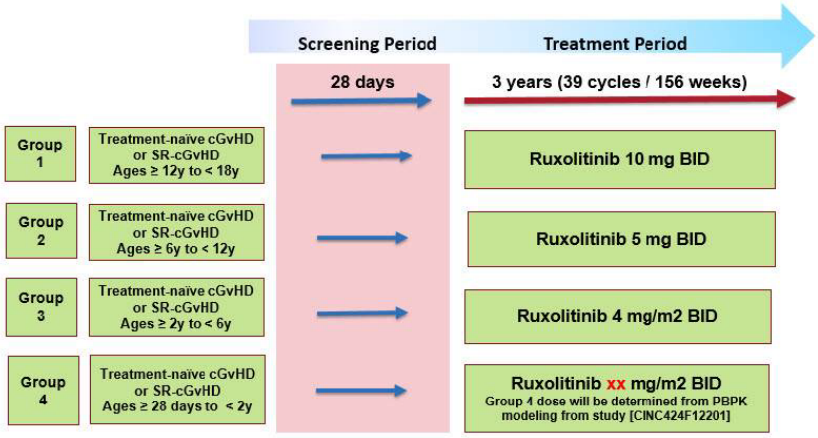
- **Ancillary analyses**

N/A

Study G12201 (REACH5) in chronic GvHD: A single-arm, Phase II multi-center study of ruxolitinib added to immunosuppressive treatment in paediatric subjects with moderate or severe cGvHD after allo-HSCT

Study G12201 was a single-arm, Phase II multi-center study of ruxolitinib added to immunosuppressive treatment in paediatric subjects with moderate or severe cGvHD after allo-HSCT. The purpose of the study was to assess the pharmacokinetics (PK), safety and activity of ruxolitinib in treatment-naive or SR cGvHD subjects aged ≥ 28 days to <18 years.

Figure 3: Study design of study G12201



Methods

- **Study Participants**

Key inclusion criteria

- Age ≥ 28 days and < 18 years
- Undergone alloHSCT from any donor source 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 2014 Consensus Criteria prior to Cycle 1 Day 1. Subjects must have been either:
    - Treatment-naive chronic GvHD subjects that have 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 therapy for chronic GvHD prophylaxis (as long as the prophylaxis was started prior to the diagnosis of chronic GvHD), or
    - Steroid refractory (SR) moderate to severe chronic GvHD as per institutional criteria, or per physician decision in case institutional criteria are not available, and were still receiving systemic corticosteroids for the treatment of chronic GvHD for a duration of < 18 months prior to Cycle 1 Day 1.

Key exclusion criteria

- Chronic SR cGvHD subjects with a prior GvHD treatment with a JAK1 or a JAK2- or a JAK1/2-inhibitor were 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 Cycle 1 Day 1 or up to 5 times the half-life of the prior JAK inhibitor, whichever is longer.

- Subjects who initiated systemic calcineurin inhibitors (CNI; cyclosporine or tacrolimus) within 3 weeks prior to start of ruxolitinib on Cycle 1 Day 1. 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.

Although inclusion of subjects aged 28 days to <2 years was planned in study G12201, no subjects in this age range were enrolled as the total sample size of 45 subjects was enrolled before availability of the PK data to select the dose and allow enrollment into Group 4 (28 days to <2 years).

- **Treatments**

Ruxolitinib treatment

Subjects received ruxolitinib twice a day continuously (in cycles of 28 days) for a planned duration of 36 months (39 cycles) unless interruption was required to manage toxicity or for progressive disease.

Details of the dose and mode of administration for each treatment group are indicated in table below.

Table 6 Dosing of ruxolitinib in study G12201

Table 9-1 Dose and treatment schedule

Investigational treatment	Age groups	Pharmaceutical form and Route of Administration	Dose	Frequency and/or Regimen
Ruxolitinib (INC424)	Group 1 ≥ 12 years old to < 18 years old	5 mg tablet* for oral use OR oral pediatric formulation	10 mg b.i.d. (2 tablets orally b.i.d.) OR 10 mg b.i.d. oral pediatric formulation**	Twice per day
Ruxolitinib (INC424)	Group 2 ≥ 6 years old to < 12 years old	5 mg tablet* for oral use OR oral pediatric formulation*	5 mg b.i.d. (1 tablet orally b.i.d.) OR 5 mg b.i.d. oral pediatric formulation**	Twice per day
Ruxolitinib (INC424)	Group 3 ≥ 2 years old to < 6 years old	5 mg tablet* for oral use OR oral pediatric formulation	4 mg/m^2 b.i.d. (either tablet orally OR oral pediatric formulation)**	Twice per day
Ruxolitinib (INC424)	Group 4 ≥ 28 days to < 2 years old	oral pediatric formulation	X mg/m^2 b.i.d. (oral pediatric formulation)** To be defined from study CINC424F12201	Twice per day

*A whole tablet for oral use may be crushed as per instructions in the pharmacy manual (if calculated dose based on BSA is not 5 mg or 10 mg, then crushing is not permitted. Tablet cannot be broken to achieve partial doses. In this case, oral pediatric formulation should be administered). Oral pediatric formulation should be dispensed according to instructions in the pharmacy manual.

Note: Crushed tablet(s) can only be administered orally and cannot be administered by nasogastric (NG) tube.

**Calculated doses should be rounded to the nearest available volume as per instructions in the pharmacy manual

Concomitant medication

Study treatment in study G12202 included i) ruxolitinib as "Investigational drug" and ii) concomitant use of corticosteroids that was required to treat treatment-naive cGvHD or SR cGvHD as "Other study treatment".

In addition, systemic CNIs could be continued after Cycle 1 Day 1 if initiated at least 3 weeks prior to the start of ruxolitinib. CNI were also allowed when initiated > 3 weeks from start of ruxolitinib.

Moreover, systemic immunosuppressive medications used for the prophylaxis of cGvHD could be continued after Cycle 1 Day 1 if initiated prior to diagnosis of cGvHD, i.e., not used as therapy but as continuation of prophylaxis.

Dose adjustments of immunosuppressive prophylactic drugs with therapeutic intent or addition of systemic immunosuppressive medications for treatment of cGvHD are not allowed.

Tapering Guidelines

Tapering of corticosteroids, CNI, and ruxolitinib will follow 2 steps: first taper systemic corticosteroids following documented CR or PR, and follow with taper of CNI/ruxolitinib.

During the Treatment Period, immunosuppression taper guidelines are:

1. **Corticosteroids:** Every effort should be made to use the minimum dose of corticosteroid that is sufficient to control cGvHD manifestation. It is recommended that a taper of corticosteroids should be attempted approximately two weeks after achieving a documented CR or PR. Guidelines are included in table below.

Table 7 Steroid tapering guidelines in study G12201

Table 6-2 Corticosteroid taper guidelines

Week (time from achieving a CR or PR)	Dose, mg/kg body weight
0	Current dose of corticosteroid every (Q) day (example 1 mg)
2	Current dose of corticosteroid (1 mg)/ decrease alternate day dose by 50%* (0.5 mg)
4	Current dose of corticosteroid (1 mg)/decrease alternate day dose by 50%* (0.25 mg)
6	Current dose of corticosteroid every other day (QOD): 1 mg every other day
8	Decrease current dose of corticosteroid by 10% every 2 weeks until off
*Alternate-day administration (Flowers and Martin, 2015)	

2. **CNI (cyclosporine or tacrolimus):** Once off systemic corticosteroids, and documented CR or PR, starting at Cycle 7 Day 1 at 25% dose reduction per month is allowed, or to be tapered per institutional practice.
3. **Ruxolitinib:** Once off systemic corticosteroids, ruxolitinib taper is allowed in subjects demonstrating a CR or PR, starting no earlier than Cycle 7 Day 1. The following guidance may be followed based on evaluation of patient condition, current dosing regimen and the clinical judgement of Investigator: a 50% dose reduction every 2 months (approximately 56 days) can be initiated.

If a cGvHD flare occurs during the taper of any immunosuppressive medications, the dose of corticosteroids may be re-escalated at the Investigator's discretion and will not be considered treatment failure.

Discontinuation of ruxolitinib.

In addition to mandatory investigational treatment discontinuation due to adverse drug reactions, investigational treatment must also be discontinued under any of the following circumstances:

- Lack of efficacy of chronic GvHD treatment.
- Lack of clinical benefit according to the Investigator.
- Underlying disease recurrence, or relapse.
- Evidence of graft failure necessitating rapid taper of immunosuppression, administration of non-scheduled DLI, stem cell boost and/or chemotherapy, or other treatment that would expectedly affect chronic GvHD.
- Subject requires a dose interruption of > 21 days from ruxolitinib.

Subjects who discontinue ruxolitinib should NOT be considered withdrawn from the study. The subject should return for the early discontinuation follow-up assessments.

The follow-up for subjects that permanently discontinue ruxolitinib early includes visits every 6 months until the subject reaches 3 years (39 cycles) from the date of their first ruxolitinib dose.

- **Objectives and Outcomes/endpoints**

Primary objectives/endpoints

Table 8 Primary objective and endpoint in study G12201

Primary objective	Endpoint
To evaluate the activity of ruxolitinib added to standard dose corticosteroids +/- CNI in pediatric subjects with moderate or severe treatment naïve chronic GvHD or SR chronic GvHD measured by overall response rate (ORR) at Cycle 7 Day 1 based on all subjects in the study.	Overall response rate (ORR) at Cycle 7 Day 1, defined as the proportion of subjects demonstrating a complete response (CR) or partial response (PR) without the requirement of additional systemic therapies for an earlier progression, mixed response or non-response. The response is assessed per NIH consensus criteria (Lee et al 2015) and scoring of response will be relative to the organ stage at the start of study treatment.

The current Primary analysis CSR is an interim analysis (data cutoff date 19-Oct-2022) from a one year analysis of study G12201. Data for the primary endpoint (ORR at Cycle 7 Day 1) was final at this timepoint.

In study G12201 it was not planned to test specific hypotheses related to the efficacy endpoint(s), but to provide estimates of efficacy endpoints, no alpha adjustment was made for the analysis of the primary endpoint. Summary statistics (frequencies and percentages) was to be provided.

cGvHD staging was performed and subjects classified into mild, moderate, and severe based on degree of organ involvement according to established NIH Consensus Criteria for cGvHD (Jagasia et al 2015).

Following the NIH working group recommendations the overall response evaluation was based on the evaluations for skin, eyes, mouth, esophagus, upper GI, lower GI, liver, lungs and joints/fascia, by the treating physician. For each post-baseline assessment comparison was made to baseline. cGvHD assessment was performed weekly during Cycle 1 and then monthly during Cycle 2-39.

- Complete response is defined as complete resolution of all signs and symptoms of cGvHD in all evaluable organs without addition of new systemic therapy, including CNIs.
- Partial response is defined as an improvement in at least one organ (e.g. improvement of 1 or more points on a 4 to 7 point scale, or an improvement of 2 or more points on a 10 to 12 point scale) without progression in other organs or sites, or initiation/addition of new systemic therapies.

- Lack of response is defined as unchanged, mixed response, or progression.
- Progression is defined as worsening of at least one organ and no improvement (CR or PR) in any other organ.
- Mixed response is a CR or PR in at least 1 organ accompanied by progression in another organ.
- Unchanged response is defined as stable disease or absence of improvement in any organ involved by cGvHD.

See table below for a summary of the rules for overall response assessment based on organ-specific evaluations at a scheduled post-baseline visit (e.g. the primary endpoint at Month 6, Cycle 7 Day 1).

Table 9 Summary of the rules for overall response assessment in study G12201

<table>
<tr><td></td><td colspan="5">Organ-specific response[1]</td></tr>
<tr><td>Skin</td><td>CR / not involved</td><td rowspan="9">PR or CR in at least one organ with baseline involvement AND no progression in any other organ (i.e. CR, PR, unchanged, no involvement), assuming overall CR has not been achieved</td><td rowspan="9">PR or CR in one or more organ(s) with baseline involvement AND progression in one or more organs (incl. new occurrence in an organ with no baseline involvement)</td><td rowspan="9">Progression in one or more organ(s) with baseline involvement OR new occurrence in an organ with no baseline involvement AND no CR or PR in any other organ</td><td rowspan="9">Organ-specific response ‘unchanged’ for all organs (incl. no involvement)</td></tr>
<tr><td>Eyes</td><td>CR / not involved</td></tr>
<tr><td>Mouth</td><td>CR / not involved</td></tr>
<tr><td>Esophagus</td><td>CR / not involved</td></tr>
<tr><td>Upper GI</td><td>CR / not involved</td></tr>
<tr><td>Lower GI</td><td>CR / not involved</td></tr>
<tr><td>Liver</td><td>CR / not involved</td></tr>
<tr><td>Lungs</td><td>CR / not involved</td></tr>
<tr><td>Joints and fascia</td><td>CR / not involved</td></tr>
<tr><td>Overall response</td><td>CR</td><td>PR</td><td>Mixed response</td><td>Progression</td><td>Unchanged response</td></tr>
<tr><td colspan="6">[1] at least one organ must be involved at baseline. Organ-specific response versus baseline status.</td></tr>
</table>

Source: Lee S, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. National institutes of health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 response criteria working group report. Biol Blood Marrow Transplant. 2015:984-999

Chronic GvHD Flare and chronic GvHD Recurrence were not considered as a treatment failure unless they required a change or addition of another systemic treatment.

- Chronic GvHD Flare was defined as any increase in symptoms or therapy for chronic GvHD after an initial response (CR or PR).
- Chronic GvHD Recurrence was defined as the return of chronic GvHD disease after tapering off study treatment due to response. For the statistical analyses, re-start of treatment for chronic GvHD was handled in the same way as addition or initiation of new systemic treatment.

The use of NIH criteria cGvHD is recommended according to the *EBMT–NIH–CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment* by Schoemans et al 2018.

The estimand framework was not used in this trial.

Secondary objectives/endpoints

The secondary endpoints included cumulative incidence of malignancy relapse/progression and OS.

Sample size

The planned sample size for the primary objective of measuring ORR at Cycle 7 Day 1 was approximately 42 subjects, regardless of age.

The sample size calculation was based on the ORR at Cycle 7 Day 1, and the calculation considered the Saw-Toothed behavior of power waving for single binomial proportion using an exact method (Chernick and Liu 2002; Published online: 01 Jan 2012). Considering the response rate of children using corticosteroids is 30% to 50% (Wolff et al 2011), the MAH assumed that the true ORR at Cycle 7 Day 1 of the study population is 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)**

Not applicable.

- **Statistical methods**

Analysis sets

If the starting dose was different from the assigned dose level due to co-administration of ruxolitinib with strong CYP3A4/CYP2C9 inhibitors, these subjects were included under the assigned dose level and considered as if they had received the full assigned dose. This applied to the both the Full Analysis Set, and the Safety Set (described below).

The **Full Analysis Set (FAS)** comprised all subjects to whom study treatment has been 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 analyzed 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 FAS was used for all baseline, demographic, and subject dispositions 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.

Analysis of the primary endpoints

The response rates for ORR at Cycle 7 Day 1, were estimated on the FAS. Confidence intervals (CIs) of 90% were calculated based on the exact method for binominal distribution.

Addition or initiation of a new systemic therapy before Cycle 7 Day 1 was considered a treatment failure, and patients were counted as non-responders.

Patients with missing assessments that prevented the evaluation of the primary endpoint were also considered non-responders. This included missing overall cGvHD response assessments at baseline and/or Cycle 7 Day 1.

As a supportive analysis, organ-specific response was calculated for all organs at Cycle 7 Day 1.

Analysis of the secondary endpoints

Duration of response (DOR) was assessed only for responders up to Cycle 7 Day 1 (i.e. all subjects with BOR = CR or PR considering response assessments up to Cycle 7 Day 1). DOR was defined as the time from first response until cGvHD progression, death, or the date of additional systemic therapies for cGvHD. Subjects without event will be censored at the date of their last response assessment prior to or at the analysis cut-off date if no events occurred on or before 12 weeks after the last GvHD

assessment. The KM method and the KM curves, medians, 3, 6, 12, 18, 24 and 36 months survival probabilities with 95% CIs were presented based on the FAS.

Reduction to low dose corticosteroids was defined as the proportion of subjects with reduction from baseline in daily corticosteroid dose to methylprednisolone-equivalent steroid dose of ≤0.2 mg/kg/day (or equivalent dose of ≤ 0.25 mg/kg/day prednisone or prednisolone) due to disease improvement at Cycle 7 Day 1. The proportion was presented based on all subjects in the FAS.

The proportion of subjects with ≥50% reduction from baseline in daily corticosteroid dose due to disease improvement at Cycle 7 Day 1 was presented based on all subjects in the FAS.

Planned subgroup analyses

The primary efficacy endpoint was summarized by treatment-naïve chronic GvHD vs. SR-chronic GvHD status to examine the homogeneity of treatment effect, provided that there were enough data for each subgroup.

Error probabilities, adjustment for multiplicity and interim analyses

No hypothesis tests were performed in this study, but 90% confidence intervals were calculated.

The results included in this report are based on an interim analysis performed when all subjects had completed 1 year of treatment or discontinued earlier. The final analysis will be performed, and the final CSR produced, after all subjects have discontinued from the study.

Changes from protocol-specified analyses

After approval of the Statistical Analysis Plan and after Data Base Lock a misspecification in the censoring rule used for the duration of response analysis has been identified that can lead to potential overestimation of the duration of response. With the underlined text in the below definition, the censoring rule was further specified to ensure that the period when events are considered corresponds to the period when those events were collected in the database, to not presume that a patient was still in response beyond last GvHD response assessment or collection of new systemic therapy. This updated definition was used for the CSR analyses. No change in the output shells were required.

Duration of Response

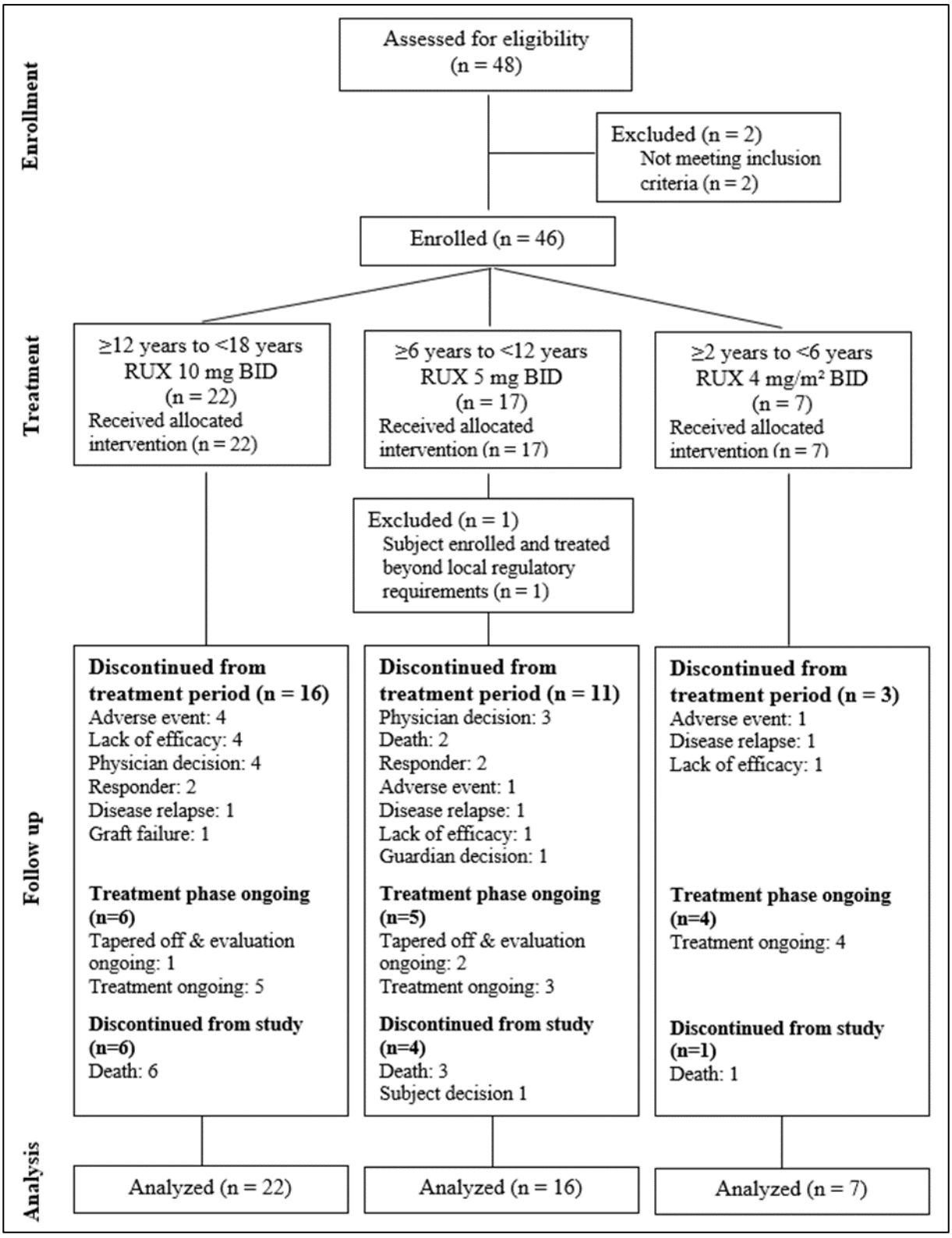
Duration of response (DOR) was assessed only for responders up to Cycle 7 Day 1 (i.e. all subjects with BOR = CR or PR considering response assessments up to Cycle 7 Day 1). DOR was defined as the time from first response until cGvHD progression, death, or the date of additional systemic therapies for cGvHD. Subjects without event were censored at the date of their last response assessment prior to or at the analysis cut-off date if no events occurred on or before 12 weeks (84 days) after the last GvHD assessment.

Analysis of duration of response for responders up to data cut-off date will be done on all subjects with BOR considering all response assessments up to End of Treatment of the subjects or data cut-off date, according to the same definition as above.

Results:

- **Participant flow**

Figure 4 Consort diagram study G12201



The median follow-up time as time from start of study treatment to last contact date or data cut-off date was 72.3 weeks.

The **Full Analysis Set (FAS)** comprised all subjects to whom study treatment has been assigned and who received at least one dose of study treatment. The FAS was used for all efficacy analyses unless otherwise specified.

- **Recruitment**

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

Study completion date: Study ongoing

Data cut-off date: 19-Oct-2022, interim analysis, Primary analysis CSR, (all subjects have completed 1 year of treatment or discontinued earlier, vs the final analysis and the final CSR that will be performed and produced after all subjects have discontinued from the study).

- **Conduct of the study**

Protocol amendments

The original study protocol was dated 12-Apr-2019 and was amended 2 times, see key features of each amendment in table below.

Table 10 Key features of protocol amendments in study G12201

Version and date	Summary of key changes
Amendment 02 09 September 2022	Public health emergency disruption proofing language inclusion Exploratory objective regarding corticosteroid-free response rates addition. Clarification on ruxolitinib treatment management and to subject withdrawal of consent.
Amendment 01 19 November 2020	Update of the guidance regarding the management of ruxolitinib Update the inclusion criteria to allow for nasogastric tube administration of the oral pediatric formulation Ruxolitinib tapering management clarification Guidance inclusion for the assessment of organ involvement and response Ruxolitinib post-trial access requirements clarification Contraception guidelines and pregnancy reporting requirements update. An assessment of benefit, risk and trial integrity related to SARS-CoV-2 virus and the COVID-19 pandemic was conducted and determined no substantial risk for subject safety or additional measures regarding study design or conduct was warranted.

Protocol deviations

Any protocol deviation occurred in 36 % of all subjects in study G1220.

According to the MAH, one of the protocol deviations led to exclusion from FAS. It was a subject that was enrolled in Italy although at the time, there was no approval in Italy for enrolment into the specific age group, thus the subject was excluded from efficacy analyses at the request of the health authorities.

According to the MAH, no other deviations led to exclusion from FAS or the Safety set.

- **Baseline data**

Table 11 Pre-transplant disease history in study G12201 (Full Analysis Set)

Characteristic Categories/Statistics	≥ 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 (%)
Primary diagnosis classification-n (%)				
Malignant-leukemia/MDS	14 (63.6)	9 (56.3)	4 (57.1)	27 (60.0)
Malignant-lymphoproliferative	0	2 (12.5)	0	2 (4.4)
Non-malignant-thalassemia	4 (18.2)	0	0	4 (8.9)
Non-malignant-severe aplastic anemia	2 (9.1)	1 (6.3)	0	3 (6.7)
Inherited metabolic disorder	2 (9.1)	2 (12.5)	2 (28.6)	6 (13.3)
Other	0	2 (12.5)	1 (14.3)	3 (6.7)
Diagnosis of underlying Malignant disease-n (%)				
Acute lymphoblastic leukemia (ALL)	9 (40.9)	5 (31.3)	1 (14.3)	15 (33.3)
Acute myelogenous leukemia (AML)	5 (22.7)	4 (25.0)	2 (28.6)	11 (24.4)
Myelodysplastic disorder (MDS)	0	0	1 (14.3)	1 (2.2)
Non-Hodgkin lymphoma	0	2 (12.5)	0	2 (4.4)
Other	0	1 (6.3)	0	1 (2.2)
Missing	8 (36.4)	4 (25.0)	3 (42.9)	15 (33.3)
Diagnosis of underlying non-Malignant disease-n (%)				
Autoimmune diseases	0	0	1 (14.3)	1 (2.2)
Histiocytic disorders	1 (4.5)	0	0	1 (2.2)
Inherited abnormalities of erythrocyte differentiation or function	1 (4.5)	2 (12.5)	0	3 (6.7)
Severe aplastic anemia	2 (9.1)	0	0	2 (4.4)
Thalassemia	4 (18.2)	0	0	4 (8.9)
Other	0	2 (12.5)	2 (28.6)	4 (8.9)
Missing	14 (63.6)	12 (75.0)	4 (57.1)	30 (66.7)
Diagnosis of underlying disease other specify -n (%)				
Chronic granulomatous disease	0	1 (6.3)	1 (14.3)	2 (4.4)
Constitutional serious bone marrow aplasia associated with Fanconi anemia	0	1 (6.3)	0	1 (2.2)
Crohn's disease	0	0	1 (14.3)	1 (2.2)
Severe congenital neutropenia	0	1 (6.3)	0	1 (2.2)
Missing	22 (100)	13 (81.3)	5 (71.4)	40 (88.9)
Time from initial diagnosis to start of study treatment (years)				
n	22	16	7	45
Mean (SD)	4.5 (4.64)	3.9 (2.78)	2.2 (1.03)	3.9 (3.70)
Median	1.9	3.2	2.4	2.5
Min-Max	0.8 - 13.6	0.7 - 9.7	0.6 - 3.4	0.6 - 13.6
CIBMTR risk assessment-n (%)				
Low	9 (40.9)	3 (18.8)	1 (14.3)	13 (28.9)
Intermediate	6 (27.3)	4 (25.0)	3 (42.9)	13 (28.9)
High	2 (9.1)	5 (31.3)	1 (14.3)	8 (17.8)
Unknown	4 (18.2)	2 (12.5)	1 (14.3)	7 (15.6)
Missing	1 (4.5)	2 (12.5)	1 (14.3)	4 (8.9)

Analyses of 'time from ... to ...' are given only for subjects with all dates available.

Seventeen subjects (38%) were treatment-naïve, and 28 subjects (62%) had SR-chronic GvHD.

Twenty seven subjects (60%) had severe cGvHD. Lung involvement was reported in 14 subjects (31%) and liver involvement in 10 subjects (22%), both mainly seen in the ≥ 12y to < 18y age group.

Overall, prior acute GvHD was reported for 33 subjects (73%), mostly with grade II acute GvHD.

The most frequent conditioning regimen in all age groups was Myeloablative, reported in overall 30 subjects (67%).

Overall, the stem cell source was bone marrow in 47% of the subjects (n=21), and peripheral blood in 47% of the subjects (n=21), and single cord blood in 7% (n=3). Stem cell source was in general similar between the different age groups.

It is noted that 13 subjects (29 %) of subjects in study G12201 were from Europe or North/South America. Twenty-two subjects (49%) were from Asia and 10 subjects (22%) from Middle east.

In principle, the study population reflects the intended indication although the sample size is limited and there is heterogeneity in multiple parameters such as age, disease history, transplant-related history, prior and concomitant medication.

Prior therapy

Sixteen subjects (36%) had **prior prophylaxis for cGvHD/SR-cGvHD**, most often CNIs (12 subjects, 27%), see table below.

Table 30 Prior prophylaxis for cGvHD/SR-cGvHD in study G12201 (Full Analysis Set)

ATC Class Preferred drug name	>=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 with at least one medication	10 (45.5)	4 (25.0)	2 (28.6)	16 (35.6)
Calcineurin inhibitors	7 (31.8)	3 (18.8)	2 (28.6)	12 (26.7)
Ciclosporin	3 (13.6)	1 (6.3)	1 (14.3)	5 (11.1)
Tacrolimus	3 (13.6)	2 (12.5)	1 (14.3)	6 (13.3)
Tacrolimus monohydrate	1 (4.5)	0	0	1 (2.2)
Glucocorticoids	4 (18.2)	1 (6.3)	0	5 (11.1)
Methylprednisolone	1 (4.5)	0	0	1 (2.2)
Prednisolone	3 (13.6)	0	0	3 (6.7)
Prednisone	1 (4.5)	1 (6.3)	0	2 (4.4)
Selective immunosuppressants	0	2 (12.5)	1 (14.3)	3 (6.7)
Mycophenolate mofetil	0	2 (12.5)	1 (14.3)	3 (6.7)

Thirty-one subjects (69%) had received **prior treatment for cGvHD**. The most frequent types of prior treatment were glucocorticoids (28 subjects, 62%) and CNI inhibitors (14 subjects, 31%), see table below.

Table 12 Prior systemic treatment for cGvHD in study G12201 (Full Analysis Set)

ATC Class Preferred drug name	≥ 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 with at least one medication	14 (63.6)	14 (87.5)	3 (42.9)	31 (68.9)
Calcineurin inhibitors	5 (22.7)	8 (50.0)	1 (14.3)	14 (31.1)
Ciclosporin	1 (4.5)	1 (6.3)	1 (14.3)	3 (6.7)
Tacrolimus	2 (9.1)	5 (31.3)	0	7 (15.6)
Tacrolimus monohydrate	2 (9.1)	2 (12.5)	0	4 (8.9)
Cd20 (clusters of differentiation 20) inhibitors	0	1 (6.3)	0	1 (2.2)
Rituximab	0	1 (6.3)	0	1 (2.2)
Glucocorticoids	13 (59.1)	12 (75.0)	3 (42.9)	28 (62.2)
Methylprednisolone	3 (13.6)	3 (18.8)	0	6 (13.3)
Methylprednisolone sodium succinate	0	1 (6.3)	1 (14.3)	2 (4.4)
Prednisolone	9 (40.9)	8 (50.0)	2 (28.6)	19 (42.2)
Prednisolone sodium succinate	1 (4.5)	0	0	1 (2.2)
Prednisone	1 (4.5)	1 (6.3)	0	2 (4.4)
Leukotriene receptor antagonists	1 (4.5)	0	0	1 (2.2)
Montelukast sodium	1 (4.5)	0	0	1 (2.2)
Nitrogen mustard analogues	1 (4.5)	0	0	1 (2.2)
Cyclophosphamide	1 (4.5)	0	0	1 (2.2)
Selective immunosuppressants	1 (4.5)	2 (12.5)	0	3 (6.7)
Mycophenolate mofetil	1 (4.5)	2 (12.5)	0	3 (6.7)

Concomitant therapy

As outlined above in section Description of trial intervention; Study treatment in study G12202 included i) ruxolitinib as "Investigational drug" and ii) concomitant use of **corticosteroids** that was required to treat treatment-naive cGvHD or SR cGvHD as "Other study treatment".

In addition, **CNIs** could be continued after Cycle 1 Day 1 if initiated at least 3 weeks prior to the start of ruxolitinib. Moreover, CNIs were also allowed when initiated > 3 weeks from start of ruxolitinib. Twenty-three subjects (51%) had concomitant CNIs.

Furthermore, systemic immunosuppressive medications used for the **prophylaxis** of cGvHD could be continued after Cycle 1 Day 1 if initiated prior to diagnosis of cGvHD, i.e., not used as therapy but as continuation of prophylaxis.

With regard to concomitant use of **CYP3A inhibitors**, 24 subjects (53%) used concomitant CYP3A4 inhibitors, most commonly voriconazole. According to the protocol, ruxolitinib dose may be reduced by 50% upon initiation of a strong CYP3A4 inhibitor or a dual CYP3A4/CYP2C9 inhibitor, and, in Protocol Amendment 2 a statement was added that if the starting dose of ruxolitinib was different from the assigned dose level due to co-administration with strong CYP3A4 inhibitors or dual CYP3A4/CYP2C9 inhibitors, these patients were included under the assigned dose level and considered that they had received the full assigned dose.

Exposure

The cut-off date for this report was after all subjects had either been exposed to ruxolitinib for at least 52 weeks or discontinued treatment prematurely.

Median exposure time to **ruxolitinib** was 55 weeks, with a minimum of 2 weeks and a maximum of 112 weeks. Median exposure was longer in treatment-naïve subjects (62 weeks) than in SR chronic GvHD subjects (50 weeks).

See table below for **duration of exposure to corticosteroids** up to Cycle 7 day 1 in study G12201.

Table 13 Duration of exposure to corticosteroids up to Cycle 7 day 1 in study G12201 (Safety Set)

	>=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
Total number of subjects receiving the drug -n (%)	20 (90.9)	14 (87.5)	6 (85.7)	40 (88.9)
Duration of exposure (weeks)				
Mean (SD)	17.3 (8.25)	16.8 (9.04)	13.8 (9.41)	16.6 (8.55)
Median	17.1	16.3	10.5	15.9
Q1 - Q3	10.9-25.6	10.4-25.6	6.7-25.6	10.4-25.6
Min - Max	3.4-25.6	1.3-25.6	4.1-25.6	1.3-25.6
Duration of exposure categories -n (%)				
<= 4 weeks	1 (4.5)	2 (12.5)	0	3 (6.7)
> 4 - 8 weeks	2 (9.1)	0	2 (28.6)	4 (8.9)
> 8 - 12 weeks	4 (18.2)	3 (18.8)	2 (28.6)	9 (20.0)
> 12 - 16 weeks	3 (13.6)	2 (12.5)	0	5 (11.1)
> 16 - 20 weeks	1 (4.5)	1 (6.3)	0	2 (4.4)
> 20 - 24 weeks	1 (4.5)	0	0	1 (2.2)
> 24 - 36 weeks	8 (36.4)	6 (37.5)	2 (28.6)	16 (35.6)
> 36 - 48 weeks	0	0	0	0
> 48 - 60 weeks	0	0	0	0
> 60 - 72 weeks	0	0	0	0
> 72 - 84 weeks	0	0	0	0
> 84 - 96 weeks	0	0	0	0
> 96 weeks	0	0	0	0
Subject-Treatment-Years	6.6	4.5	1.6	12.7

Subject-Treatment-Years is the sum of each subject's treatment exposure in years.

Overall, the mean duration of exposure to **CNIs** was 47 weeks. Mean exposure to CNIs was highest in the ≥ 12 y to < 18 y age group (55 weeks, SD: 38.50), followed by the ≥ 6 y to < 12 y age group (45 weeks, SD: 31.68) and the ≥ 2 y to < 6 y age group (27 weeks, SD: 24.75).

- **Numbers analysed**

Table 14 Analysis sets in study G12201 (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/m^2 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-chronic GvHD	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-chronic GvHD	12 (52.2)	12 (66.7)	4 (57.1)	28 (58.3)
Pharmacokinetic analysis set	21 (91.3)	15 (83.3)	7 (100)	43 (89.6)
Treatment-naive	9 (39.1)	3 (16.7)	3 (42.9)	15 (31.3)
SR-chronic GvHD	12 (52.2)	12 (66.7)	4 (57.1)	28 (58.3)
Listing only set	0 (0.0)	1 (5.6)	0 (0.0)	1 (2.1)
Treatment-naive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SR-chronic GvHD	0 (0.0)	1 (5.6)	0 (0.0)	1 (2.1)

- **Outcomes and estimation**

The Full Analysis Set (FAS) comprised all subjects to whom study treatment has been assigned and who received at least one dose of study treatment. The FAS was used for all efficacy analyses in study G12202 unless otherwise specified.

The cut-off date for this report (interim analysis, Primary analysis CSR G12201) was 19-Oct-2022, when all subjects had either been exposed to ruxolitinib for at least 52 weeks 1 year or discontinued treatment prematurely.

In the current submission, efficacy evaluations in paediatric subjects with cGvHD were based on the pooled data from the

i. Paediatric Study G12201 (REACH 5, N=45), and from

ii. Adolescent subjects treated with ruxolitinib treatment in Study D2301 (REACH 3, N=4)

Primary endpoint – ORR at Cycle 7 day 1

Table 15 ORR at Cycle 7 day 1 in the Pooled chronic GvHD paediatric subjects G12201 + D2301

	Study G12201				Study D2301	Studies G12201+D2301
	≥12y - <18y 10mg b.i.d. N=22 n (%)	≥6y - <12y 5mg b.i.d. N=16 n (%)	≥2y - <6y 4mg/m² b.i.d. N=7 n (%)	All subjects N=45 n (%)	≥12y - <18y 10mg b.i.d. N=4 n (%)	Total pediatric subjects N=49 n (%)
Overall response						
Responders						
Complete Response (CR)	1 (4.5)	2 (12.5)	1 (14.3)	4 (8.9)	0	4 (8.2)
Partial Response (PR)	7 (31.8)	6 (37.5)	1 (14.3)	14 (31.1)	3 (75.0)	17 (34.7)
Non-responders						
Unchanged Response	2 (9.1)	2 (12.5)	1 (14.3)	5 (11.1)	0	5 (10.2)
Mixed response	2 (9.1)	0	0	2 (4.4)	0	2 (4.1)
Progression	0	0	0	0	0	0
Other *	0	0	0	0	0	0
Unknown	10 (45.5)	6 (37.5)	4 (57.1)	20 (44.4)	1 (25.0)	21 (42.9)
Death	2 (9.1)	1 (6.3)	1 (14.3)	4 (8.9)	0	4 (8.2)
Early discontinuation	7 (31.8)	3 (18.8)	2 (28.6)	12 (26.7)	0	12 (24.5)
Missing visits	1 (4.5)	2 (12.5)	1 (14.3)	4 (8.9)	1 (25.0)	5 (10.2)
Overall Response Rate (ORR: CR+PR)	8 (36.4)	8 (50.0)	2 (28.6)	18 (40.0)	3 (75.0)	21 (42.9)
90% CI for ORR	(19.6, 56.1)	(27.9, 72.1)	(5.3, 65.9)	(27.7, 53.3)	(24.9, 98.7)	(30.8, 55.6)

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

It is noted that the MAH use 90% CI for the efficacy results in the SmPC section 5.1.

For the primary endpoint (ORR at Cycle 7 day 1) in study G12201, there was a noticeably high rate (44%, n=20) of missing and thus unknown assessments of response. The most common reason for non-response was early discontinuation (12 subjects, 27%). Most of these subjects stopped before Cycle 7 day 1 due to lack of efficacy (n=5) or disease relapse (n=2). Two subjects discontinued due to response and physician decision with a CR after Cycle 5 and Cycle 4, respectively. Since no assessment was done at Cycle 7 Day 1 these subjects were not considered as responders for the primary endpoint. Four subjects were considered non-responders due to missing visits. Assessments for these subjects were done outside of the allowed time window for Cycle 7 Day 1. Three of the 4 subjects had PR (based on BOR) assessed 2 or 3 days after the time window.

The ORR at Cycle 7 Day 1 was numerically similar for treatment-naïve subjects (41%, 90% CI: 21, 64) and SR-chronic GvHD subjects (39%, 90% CI: 24, 57) in study G12201.

ORR at Cycle 7 Day 1 was higher for subjects with moderate chronic GvHD (53%, 90% CI: 31, 74) than for subjects with severe chronic GvHD (32%, 90% CI: 18, 49) in study G12201.

Selected secondary endpoints

Overall survival (OS) was defined as the time from the date of treatment assignment (Study G12201) or the date of randomization (Study D2301) to date of death due to any cause. Deaths occurred in 10 (20%) subjects, all of which were reported in Study G12201. The 12-month OS probability was 85% (95% CI: 72, 93) and the 24-month OS probability was 76% (95% CI: 58, 87). The Kaplan-Meier estimated median OS was not reached in the Pooled chronic GvHD paediatric subjects.

Analysis for **malignancy relapse/recurrence (MR)** included 33 subjects who had underlying malignant hematological disease, among whom, MR was reported in 3 (9%) subjects and the competing risk of deaths due to non-malignancy relapse/progression was reported in 7 (21%) subjects.

Regarding **tapering of corticosteroids** in study G12201, 17 subjects (43%) had stopped or tapered off corticosteroids completely (including due to e.g. AEs), 27 subjects (68%) received a low dose of corticosteroids (≤ 0.2 mg/kg/day), and 30 subjects (75%) had tapered corticosteroid dose by ≥ 50% from Baseline at least once by Cycle 7 Day 1.

- **Ancillary analyses**

Not applicable.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 35. Summary of Efficacy for trial F12201

Title: A Phase I/II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in paediatric subjects with Grade II-IV acute graft vs. host disease after allogeneic hematopoietic stem cell transplantation.			
Study identifier	REACH4, CINC424F12201, EudraCT no. 2018-000422-55, NCT03491215		
Design	Open-label, single-arm, multi-center, phase I/II study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Study initiation date: 21-Feb-2019, completed 02-Feb-2023 Not applicable Not applicable
Hypothesis	Exploratory, no hypothesis tests were performed, the sample size was determined so that a 90% confidence interval could rule out an ORR under 60% in study F12201		
Treatments groups	Acute GvHD, steroid refractory or treatment-naïve subjects		10 mg b.i.d. (≥ 12 to < 18 years) 5 mg b.i.d. (≥ 6 to < 12 years) 4 mg/m2 b.i.d. (≥ 2y to < 6 years)
Endpoints and definitions	Primary endpoint	ORR at day 28(overall response rate)	Proportion of patients demonstrating a complete response (CR) or partial response (PR) without requirement for additional systemic therapies
	Key secondary endpoint	ORR at day 56	Proportion of patients who achieved a complete response (CR) or partial response (PR) at Day 28 and maintain a CR or PR at Day 56
Database lock	DCO 02-Feb-2023		
Results and Analysis			
Analysis description	**Final Analysis**		

Title: A Phase I/II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in paediatric subjects with Grade II-IV acute graft vs. host disease after allogeneic hematopoietic stem cell transplantation.		
Study identifier	REACH4, CINC424F12201, EudraCT no. 2018-000422-55, NCT03491215	
Analysis population and time point description	The Full Analysis Set (FAS) comprised all subjects to whom study treatment was assigned and who received at least one dose of study treatment. Efficacy Evaluable Set included all subjects to whom study treatment was assigned at the RP2D of ruxolitinib and who received at least one dose of study treatment at that dose level. All subjects were treated based on the assigned dose level that was confirmed as the RP2D of each age group. Therefore, the Efficacy Evaluable Set was the same as the FAS. The final analysis took place once all subjects had completed the Long-Term Follow-Up period.	
Descriptive statistics and estimate variability	Treatment group	Acute GvHD
	Number of subject	n=45
	ORR at day 28, % (90% CI)	84% (90%CI: 73, 93)*
	ORR at day 56, % (90% CI)	67% (90%CI 53, 78)
Notes	*The ORR at day 28 was 69% (90% CI: 43, 89) for Treatment-naïve subjects n=13, and 91% (90% CI: 78, 97) for SR-GvHD subjects n= 32	

Table 36. Summary of Efficacy for trial G12201

Title: Phase II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in paediatric subjects with moderate and severe chronic graft vs. host disease after allogeneic stem cell transplantation.			
Study identifier	REACH5, CINC424G12201, EUDRACT number 2018-003296-35, NCT03774082		
Design	Open-label, single-arm, multi-center, phase II study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Study initiation date: 20-May-2020 (ongoing) Not applicable Not applicable
Hypothesis	Exploratory, no hypothesis tests were performed, the sample size was determined so that a 90% confidence interval could rule out an ORR under 50% in study G12201.		
Treatments groups	Chronic GvHD, steroid refractory or treatment-naïve subjects		10 mg b.i.d. (⩾ 12 to < 18 years) 5 mg b.i.d. (⩾ 6 to < 12 years) 4 mg/m2 b.i.d. (⩾ 2y to < 6 years)
Endpoints and definitions	Primary endpoint	ORR at Cycle 7 Day 1 (overall response rate)	The proportion of patients demonstrating a complete response (CR) or partial response (PR) without the requirement of additional systemic therapies
Database lock	DCO 19-Oct-2022		
Results and Analysis			

Title: Phase II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in paediatric subjects with moderate and severe chronic graft vs. host disease after allogeneic stem cell transplantation.		
Study identifier	REACH5, CINC424G12201, EUDRACT number 2018-003296-35, NCT03774082	
Analysis description	**Interim Analysis**	
Analysis population and time point description	The Full Analysis Set (FAS) comprised all subjects to whom study treatment has been assigned and who received at least one dose of study treatment The FAS was used for all efficacy analyses. The interim analysis took place once all subjects had completed 1 year of treatment or discontinued earlier.	
Descriptive statistics and estimate variability	Treatment group	Chronic GvHD
	Number of subject	N=45
	ORR at Cycle 7 day 1 % (90% CI)	40% (90%CI: 28, 53)*
Notes	*The ORR at Cycle 7 day 1 was 41% (90% CI: 21, 64) in Treatment-naïve subjects n=17, and 39% (90% CI: 24, 57) in SR-chronic GvHD subjects n=28	

2.6.5.3. Clinical studies in special populations

Not applicable.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.6.5.6. Supportive study(ies)

Not applicable.

2.6.6. Discussion on clinical efficacy

Ruxolitinib is currently approved for the treatment of patients aged 12 years and older with acute GvHD (aGvHD) or chronic GvHD (cGvHD) who have inadequate response to corticosteroids or other systemic therapies (steroid refractory, SR). This approval was based on two randomized controlled studies, C2301 and D2301 for acute and chronic GvHD, respectively.

In the current procedure, the MAH has applied for an extension of indication for the use of ruxolitinib in paediatric patients aged 28 days or older with acute or chronic GvHD, both in treatment-naïve (TN) and SR setting.

Design and conduct of clinical studies

Efficacy claims are based on PK and clinical outcomes of two paediatric single-arm studies (Study F12201 and G12201), and additional analyses on data pooled from (i) Study F12201 and ruxolitinib treated adolescents in the randomized Study C2301 for aGvHD, and (ii) Study G12201 and ruxolitinib treated adolescents in the randomized in Study D2301 for cGvHD.

Study design and Study population

Study F12201 was a Phase I/II, single-arm, study of ruxolitinib added to corticosteroids in subjects aged ≥ 28 days to <18 years with grade II-IV aGvHD with the purpose to assess safety, efficacy, and pharmacokinetics of ruxolitinib with corticosteroids in aGvHD.

- Treatment-naïve aGvHD subjects were allowed to have received 72h of prior systemic corticosteroid treatment after the onset of aGvHD.
- SR-aGvHD subjects were allowed to have received one prior systemic treatment for aGvHD in addition to corticosteroids. SR-aGvHD was diagnosed per institutional criteria or per physician decision in case institutional criteria were not available.

Study G12201 was a Phase II, single-arm, study of ruxolitinib added to corticosteroids in subjects aged ≥ 28 days to <18 years with moderate or severe cGvHD with the purpose to assess safety, activity, and pharmacokinetics of ruxolitinib with corticosteroids in cGvHD.

- Treatment-naive cGvHD subjects were allowed to have received 72h of prior systemic corticosteroid treatment after the onset of cGvHD.
- SR-cGvHD subjects were allowed to have received systemic calcineurin inhibitors (CNIs) if initiated at least 3 weeks prior to the start of ruxolitinib. SR-cGvHD was diagnosed per institutional criteria, or per physician decision in case institutional criteria are not available.

Subjects with Grade I aGvHD or mild cGvHD were not eligible. In clinical practice these patients would rarely be offered systemic treatment, but rather topical alternatives. Moreover, responses observed across GvHD stages did not indicate worse outcomes with lower grades in study F12201 and G12201. It is therefore considered acceptable not to specify the grade or severity of GvHD in the indication. For details with regard to GvHD grade and type (acute or chronic) of the studied population, a reference to SmPC section 5.1 is included in the sought indication. This is in line with the currently approved indication for adults/adolescents with acute or chronic GvHD.

Study treatment

The following dosing of ruxolitinib was used in the phase 2 part of study F12201 and in study G12201;

- 10 mg b.i.d. (≥ 12 to < 18 years) Group 1, which is the same as the approved dose in adults/adolescents.
- 5 mg b.i.d. (≥ 6 to < 12 years) Group 2 and
- 4 mg/m2 b.i.d. (≥ 2y to < 6 years) Group 3.

No subjects in age group 4 (< 2 years) were enrolled in study F12201 or G12201. This was since enrollment was completed before availability of PK data to select the dose for this age group. Thus, no clinical data are available for subjects <2 years. The proposed dose for these subjects was instead predicted by PBPK modeling.

Please refer to the assessment of PK for further discussion on the proposed dosing and establishment of PK bridge to the adult efficacy demonstration in SR aGvHD/study C2301 and SR cGvHD/study D2301.

In study F12201, concomitant treatment with corticosteroids +/- CNI was required in both treatment-naïve and SR aGvHD subjects. In addition, aGvHD prophylaxis could be continued if started prior to diagnosis of aGvHD. Thus, these single arm trials did not investigate ruxolitinib monotherapy, but rather its use as add-on to medicines known to be efficacious against GvHD.

The planned duration of ruxolitinib treatment in study F12201 was 24 weeks. Tapering of corticosteroids could be initiated from Day 7 in patients demonstrating a PR or CR. CNI and ruxolitinib tapering was allowed in patients demonstrating a PR or CR, once off corticosteroids. The tapering of ruxolitinib could start from Day 56.

In study G12201, concomitant treatment with corticosteroids was required in both treatment-naive and SR cGvHD. In addition, CNIs could be continued after Cycle 1 Day 1 if initiated at least 3 weeks prior to the start of ruxolitinib and CNIs were also allowed if initiated > 3 weeks from start of ruxolitinib. Moreover, cGvHD prophylaxis could be continued if started prior to diagnosis of cGvHD. The planned duration of ruxolitinib treatment was 36 months/39 cycles (in cycles of 28 days). Tapering of corticosteroids was recommended approximately two weeks after achieving a CR or PR. CNI and ruxolitinib tapering was allowed after Cycle 7 Day 1 in patients demonstrating a PR or CR, once off corticosteroids.

In the SmPC section 4.2, it is clarified that ruxolitinib can be added to corticosteroids and/or CNIs in GvHD.

In addition, it is specified in SmPC section 5.1 that patients were treated with ruxolitinib and corticosteroids +/- CNI in both study F12201 and G12201.

Objectives/endpoints

The primary endpoint in study F12201 was ORR at day 28 using NIH criteria as described by Harris et al 2016. In study G12201, the primary endpoint was ORR at Cycle 7 Day 1 (i.e., at 6 months) using NIH Consensus Criteria described by Jagasia et al 2015.

These endpoints and the tools for response assessments, are in line with the primary endpoints in study C2301 and D2301 which formed the basis for the approval of ruxolitinib on acute and chronic GvHD in adults/adolescents, respectively.

Statistical methods

In both studies (F12201 and G12201), the primary endpoints were analysed on all subjects. Subjects with missing endpoint data were considered non-responders. In study F12201, subjects were also considered to be non-responders if they discontinued the study treatment. In study G12201, addition or initiation of new systemic treatment was analysed as non-response. This type of non-response imputation is acceptable because it is conservative, meaning that it may underestimate the ORR.

The MAH claims that the studies did not test any statistical hypotheses, but this is not agreed. Although p-values were not calculated, the sample sizes were determined so that a 90% confidence interval could rule out an ORR under 60% in study F12201 and an ORR under 50% in study G12201. These are success criteria that corresponds to a hypothesis test of whether ORR is greater than 60% or 50%. Study F12201 succeeded in meeting its success criterion but study G12201 did not. Even so, a further discussion of this matter is not needed because the effect of ruxolitinib cannot formally be separated from the effect of concomitant medications in either of these single-arm studies.

The MAH did not justify the use of 90% confidence intervals rather than the conventional 95%. Although 95% confidence intervals are generally expected, a reanalysis was not considered necessary in this case because the study was considered exploratory.

In the phase II part of study F12201, 5 out of the 45 included subjects had previously participated in the phase I dose-finding part of the trial, where they received the confirmed RP2D. This kind of practice (reuse of subjects) is generally discouraged because the second part should be independent from the first in order to confirm its results. Nevertheless, this is considered a minor issue because the trial is considered exploratory rather than confirmatory.

Conduct of the studies

In study F12201, 7 subjects were administered prohibited concomitant medication during treatment period. These protocol deviations did not have a significant impact on interpretation of the primary endpoint.

Any protocol deviation occurred in 36% of all subjects in study G12201.

Efficacy data and additional analyses

The efficacy results for **aGvHD** (presented in SmPC section 5.1) are based on efficacy data from the FAS in study F12201 (n=45).

The efficacy results for **cGvHD** (presented in SmPC section 5.1) are based on efficacy data from the FAS in study G12201 (n=45).

These are paediatric data and are presented despite not isolating drug effects. This is noted in the SmPC text.

Study F12201

Participant flow

At the time of data cut-off, 22 subjects (49%) had completed study treatment and 23 subjects (51%) had discontinued from treatment period. The most common reason for early treatment discontinuation was lack of efficacy (27%, n = 12) and adverse event (22%, n = 10).

Baseline data

Five out of the 45 included subjects had previously participated in the phase I dose-finding part of the trial, where they received the confirmed RP2D.

Thirty two subjects (71%) had SR aGvHD and 13 subjects (29%) were treatment-naïve. The majority (64%, n=29) had Grade II aGvHD, while 27% (n= 12) had grade III and 9% (n=4) hade grade IV. Twenty-seven subjects (60%) had underlying malignancy, most frequently leukemia.

Thirty nine subjects (87%) received prior aGvHD prophylaxis which started and ended prior to study treatment.

The applicant has clarified that subjects (n=3) with relatively long time (more than 100 days) from aGvHD diagnosis to treatment start had an aGvHD diagnosis at study entry, and not a chronic GvHD or GvHD overlap syndrome diagnosis.

Ninety percent (n=40) of subjects had a duration of exposure to corticosteroids that exceeded 28 days, i.e., at least until the assessment of primary endpoint. In addition, overall 89% received concomitant CNIs. The median exposure to CNIs of 111 days (min: 1, max: 365). For comparison, median exposure time to ruxolitinib was 117 days (min: 8, max: 342). Thus, this study was not designed to isolate the effect of ruxolitinib.

In addition to concomitant corticosteroid and CNIs, 27% (n=12) of subjects in study F12201 had "additional systemic aGvHD therapy" after the start of the ruxolitinib treatment including 3 subjects (7%) who had interleukin inhibitors and 7 subjects (16%) who had selective immunosuppressants such

as mycophenolate mofetil, abatacept, ATG and sirolimus. The MAH clarified that all the 4 patients that started additional aGvHD treatment before the time point for primary endpoint assessment were classified as non-responders and by that did not impact the interpretability of efficacy attributed to study treatment.

Further, 27% (n=12) of subjects in study F12201 received aGvHD prophylaxis medication on or after the ruxolitinib treatment start date. The MAH clarified that only 3 patients had aGvHD prophylaxis (other than CNI, which were permitted as concomitant treatment) ongoing at the timepoint for evaluation of the primary endpoint. This is not considered to have a significant impact on the overall efficacy results.

Outcomes and estimation

The primary endpoint ORR at Day 28 was 84% (90%CI: 73, 92) in the pooled paediatric subjects (n=50) with aGvHD, with CR reported in 50% of subjects. The ORR at Day 28 showed consistency (>80%) across the age groups.

A numerically lower ORR at day 28 in treatment-naïve (ORR 69%, 90% CI: 43, 89) vs. SR aGvHD subjects is noted (ORR 91%, 90% CI: 78, 97). The MAH argues that this difference may be attributed to baseline organ involvement and organ stage, pre-transplant disease history and early discontinuation rate among subjects with treatment-naïve or SR aGvHD.

Among the 32 **SR** aGvHD patients in study F12201, 10 patients were reported to be off corticosteroids at Day 56. Eight of these 10 patients completed steroid taper following response and were complete responders at the end of treatment in the absence of corticosteroid treatment, suggesting a maintained response to ruxolitinib.

Among the **TN** aGvHD patients in study F12201, 7 out of 13 (54%) were off corticosteroids at Day 56. Out of these 7 TN patients, 6 were complete responders at the end of treatment. Of note, the primary endpoint was ORR at Day 28.

Given the add-on design this single-arm trial, it cannot be ascertained that the objective responses that were recorded in SR and treatment-naïve aGvHD subjects in study F12201, were due to the efficacy of ruxolitinib. In section 5.2 of the SmPC, it is stated that the design of study F12201 and G12201 does not isolate the contribution of ruxolitinib to overall efficacy.

Study G12201

Participant flow

At the time of data-cut-off, 15 subjects (33%) had treatment phase ongoing, and 30 subjects (67%) had discontinued treatment at the time of data-cut-off. None of the subjects enrolled in study G12201 had completed treatment.

The most common reason for treatment discontinuation was Physician decision in 7 subjects (16%) of which 4 subjects had a final assessment of CR och PR and either switched to new treatment or discontinued ruxolitinib due to medical reasons, while 3 subjects had either unchanged response or progressive disease and required new treatment. In addition, 6 subjects (13%) discontinued ruxolitinib due to Lack of efficacy, and 6 subjects (13%) due to AEs.

Baseline data

Seventeen subjects (38%) were treatment-naïve, and 28 subjects (62%) had SR cGvHD.

Twenty seven subjects (60%) had severe cGvHD and 18 subjects (40%) had moderate cGvHD.

Thirty subjects (67%) had underlying malignancy, most frequently leukemia.

Thirty six percent (n=16) of subjects had a duration of exposure to corticosteroids of > 24 to 36 weeks, i.e., until or beyond the assessment of the primary endpoint.

In addition to concomitant corticosteroids, 51% (n=23) of subjects in study G12201 had concomitant CNIs. The median duration of exposure to CNIs was 54 weeks (min:1, max:110). For comparison, median exposure to ruxolitinib was 55 weeks (min:2, max, 112). The MAH clarified that 14 patients (31%) were taking CNI at the time of primary endpoint (C7D1). Although the use of CNI (as defined in the protocol) was allowed in study G12201, it does hamper the possibility to isolate the effect of ruxolitinib in paediatric cGvHD.

Further, 36% (n=16) of subjects had prior prophylaxis for cGvHD/SR-cGvHD. According to the protocol, medications used for the cGvHD prophylaxis could be continued after start with ruxolitinib treatment. The MAH clarified that 7 patients had prophylactic therapy still ongoing at start of study treatment. Although the use of prophylaxis for cGvHD/SR-cGvHD (as defined in the protocol) was allowed, it highlights the fact that study G12201 was not appropriately designed to clearly isolate the effects of ruxolitinib in paediatric cGvHD.

Subjects with prior JAK1/2-inhibitor GvHD treatment who had achieved complete or partial response and had been off JAK inhibitor treatment for at least 4 weeks, were eligible for study G12201. However, the MAH clarified that no patients had received prior treatment with a JAK inhibitor.

Outcomes and estimation

The cut-off date for this report was 19-Oct-2022, when all subjects had either been exposed to ruxolitinib for at least 1 year or discontinued treatment prematurely.

Data for the primary endpoint (ORR at Cycle 7 Day 1, i.e., after 6 months of ruxolitinib treatment) was final in this interim analysis, since all subjects have completed 6 months of treatment.

The ORR at Cycle 7 Day 1 was 43% (90%CI: 31, 56) in the pooled paediatric subjects (n=49). Response rates across the age groups ranged from 29% to 50%, with wide and overlapping confidence intervals.

The ORR at Cycle 7 Day 1 was numerically similar for treatment-naïve subjects (41%, 90% CI: 21, 64) and SR-cGvHD subjects (39%, 90% CI: 24, 57).

Response rates across the age groups in study G12201 ranged from 29% to 50%, with wide and overlapping confidence intervals that according to the MAH suggests no significant difference in response among the age groups.

The MAH stated that a higher number of subjects with severe disease in the ≥ 12y to < 18y age group of Study G12201 may explain the slightly lower ORR (36%) observed in this age group, and that the lower ORR (29%) in the ≥ 2y to < 6y age group is likely due to a high rate (57%) of missing assessment of response (missing visit, early discontinuation, and death) together with low number of subjects in that age group (n=7). The response rate was higher (75%) in adolescent subjects from Study D2301, however, there were only 4 subjects in this age group which makes the interpretation difficult. In the Rapporteurs view, the limited sample sizes prevent any firm conclusions on the overall response rates in different age groups in study G12201 to be drawn. The CR ranged from 5-14% in the different age groups.

Among the 28 **SR** cGvHD patients in study G12201, 9 patients achieved corticosteroid free response (defined as any CR or PR in the absence of corticosteroid treatment in the last 4 weeks before the assessment).

Among the 17 **treatment-naïve** patients in study G12201, the MAH reports that corticosteroid-free response rate measured at any time up to data cut-off date was 47.1%, i.e., in 8 out of the 17 TN cGvHD patients.

Further, 5 patients in study G12201 started ruxolitinib treatment without corticosteroids of which two were TN patients. These two TN patients showed sustained response of CR/PR for 12 and 18 months.

Given the add-on design this single-arm trial, it cannot be ascertained that the objective responses that were recorded in SR and treatment-naïve cGvHD subjects in study G12201, were due to the efficacy of ruxolitinib. The effect of ruxolitinib cannot be separated from the effect of concomitant medications in either of the single-arm studies.

Use in treatment naïve patients

There is no adult indication for TN aGvHD or TN cGvHD. Thus, the use of ruxolitinib in paediatric TN aGvHD and TN cGvHD would require not just a PK bridge between paediatrics and adults, but also an extrapolation of benefit from the steroid refractory setting in adolescents and adults to the treatment-naïve setting in children.

There is little doubt that Jakavi, having shown benefit in SR disease in adults, will also have activity in treatment naïve patients. However, it is unclear how this activity would translate into benefit. Either Jakavi could be used as add-on to steroids hoping to increase ORR, or it could be used as a steroid-sparing agent, reaching the same treatment goal while reducing steroid side effects. There is no efficacy demonstration or -metric for either of these effects with Jakavi. Therefore, there can be no PK/PD bridge from the SR to the naïve setting.

The conducted paediatric study program, with noticeably limited number of TN patients in single-arm trials with add-on design, does not allow for clear isolation of the effects and benefit of ruxolitinib in (a) TN acute GvHD or (b) TN chronic GvHD.

In summary, the proposed use in TN patients is not approvable and consequently the applicant has removed TN patients from the proposed indication.

2.6.7. Conclusions on the clinical efficacy

There is biological rationale for a benefit of ruxolitinib in paediatric patients < 2 years of age with acute or chronic GvHD in both in SR and treatment-naïve setting.

It is acknowledged that the presented observations from study F12201 and G12201 suggest that ruxolitinib is not devoid of efficacy in paediatric acute and chronic GvHD. This is anticipated. However, the studies were not designed to isolate the effect of ruxolitinib. Thus, the appropriateness of the dose and the B/R balance cannot be determined on their basis. The MAH's claims ultimately rest on the establishment of a PK bridge to the adult efficacy demonstration in SR acute and chronic GvHD (see PK assessment).

Since (i) there is no adult indication or efficacy demonstration for TN acute or chronic GvHD and (ii) the conducted paediatric study program does not allow for an isolation of the effects and benefit of ruxolitinib in TN GvHD patients, the use of ruxolitinib in this setting is not approvable. Thus, the applicant withdrew the claim to include TN patients in the indication. The final indication in GvHD includes only patients who have inadequate response to corticosteroids or other systemic therapies.

2.6.8. Clinical safety

The safety data set included all patients who received at least one dose of study medicine in studies F12201 and G12201, as well as C2301 and D2301. The safety database in acute GvHD included 51 subjects from ≥2 to <18 years, the safety data base for chronic GvHD includes 56 subjects from ≥2 to <18 years. There was no subject younger than 2 years enrolled to the studies.

The main studies F12201 and G12201 were open-label, uncontrolled and single arm. Such design of studies precludes thorough evaluation of safety. Studies C2301 and D2301 were randomized, open label, where 6 and 10 paediatric subjects aged ≥12 to <18 years have been enrolled, respectively. Having considered the well-established safety profile of the product in other indications and patient groups, the safety set is however considered acceptable.

2.6.8.1. Patient exposure

Table 37 Duration of exposure to ruxolitinib in acute GvHD (Safety set)

	Study F12201				Study C2301	Studies F12201+ C2301
	≥12y-<18y 10 mg b.i.d. N=18	**≥6y-<12y 5 mg b.i.d. N=12**	**≥2y-<6y mg/m² b.i.d. N=15**	**Total paediatric subjects N=45**	**≥12y-<18y 10 mg b.i.d. N=6**	**Total paediatric subjects N=51**
Total number of subjects receiving the drug, -n (%)	18 (100)	12 (100)	15 (100)	45 (100)	6 (100)	51 (100)
Duration of exposure (weeks)						
Mean (SD)	16.9 (14.70)	14.3 (8.76)	21.2 (11.88)	17.6 (12.45)	15.2 (13.91)	17.4 (12.51)
Median	11.6	17.6	20.0	16.7	14.2	16.7
Q1-Q3	4.3–24.6	6.4–22.5	15.9–29.1	6.6–23.9	2.6–24.1	6.0–23.9
Min – Max	1.3-48.9	1.1-23.9	4.1-41.0	1.1-48.9	1.6-34.6	1.1-48.9
Duration of exposure categories -n (%)						
≤ 4 weeks	4 (22.2)	2 (16.7)	0	6 (13.3)	2 (33.3)	8 (15.7)
> 4 - 8 weeks	2 (11.1)	3 (25.0)	3 (20.0)	8 (17.8)	1 (16.7)	9 (17.6)
> 8 - 12 weeks	3 (16.7)	0	0	3 (6.7)	0	3 (5.9)
> 12 - 16 weeks	1 (5.6)	0	1 (6.7)	2 (4.4)	0	2 (3.9)
> 16 - 20 weeks	1 (5.6)	3 (25.0)	4 (26.7)	8 (17.8)	0	8 (15.7)
> 20 - 24 weeks	2 (11.1)	4 (33.3)	3 (20.0)	9 (20.0)	1 (16.7)	10 (19.6)
> 24 - 36 weeks	3 (16.7)	0	1 (6.7)	4 (8.9)	2 (33.3)	6 (11.8)
> 36 - 48 weeks	1 (5.6)	0	3 (20.0)	4 (8.9)	0	4 (7.8)
> 48 - 60 weeks	1 (5.6)	0	0	1 (2.2)	0	1 (2.0)
Subject-Treatment-Years	5.8	3.3	6.1	15.2	1.7	17.0

Subject-Treatment-Years is the sum of each subject's treatment exposure in years. Source:

Table 38 Duration of exposure to ruxolitinib in chronic GvHD (Safety set)

	Study G12201				Study D2301	Studies G12201+D2301
	≥12y-<18y 10 mg b.i.d. N=22	**≥6y-<12y 5 mg b.i.d. N=16**	**≥2y-<6y 4mg/m² b.i.d. N=7**	**Total paediatric subjects N=45**	**≥12y-<18y 10 mg b.i.d. N=10**	**Total paediatric subjects N=55**
Total number of subjects receiving the drug -n (%)	22 (100)	16 (100)	7 (100)	45 (100)	10 (100)	55 (100)

	Study G12201				Study D2301	Studies G12201+D2301
	≥12y-<18y 10 mg b.i.d. N=22	≥6y-<12y 5 mg b.i.d. N=16	≥2y-<6y 4mg/m^2 b.i.d. N=7	Total paediatric subjects N=45	≥12y-<18y 10 mg b.i.d. N=10	Total paediatric subjects N=55
Duration of exposure (weeks)						
Mean (SD)	50.2 (39.29)	51.8 (28.64)	39.5 (29.63)	49.1 (33.97)	77.8 (56.45)	54.3 (39.96)
Median	41.5	59.1	58.9	55.1	65.1	57.1
Q1-Q3	13.1-87.9	30.6-70.6	7.1-63.0	13.1-75.3	40.0-137.3	13.1-78.4
Min - Max	2.3-112.1	2.1-101.0	6.3-68.9	2.1-112.1	2.6-155.4	2.1-155.4
Duration of exposure categories -n (%)						
≤ 4 weeks	2 (9.1)	1 (6.3)	0	3 (6.7)	1 (10.0)	4 (7.3)
> 4 - 8 weeks	1 (4.5)	1 (6.3)	2 (28.6)	4 (8.9)	0	4 (7.3)
> 8 - 12 weeks	1 (4.5)	0	1 (14.3)	2 (4.4)	0	2 (3.6)
> 12 - 16 weeks	2 (9.1)	1 (6.3)	0	3 (6.7)	1 (10.0)	4 (7.3)
> 16 - 20 weeks	3 (13.6)	1 (6.3)	0	4 (8.9)	0	4 (7.3)
> 20 - 24 weeks	0	0	0	0	0	0
> 24 - 36 weeks	2 (9.1)	0	0	2 (4.4)	0	2 (3.6)
> 36 - 48 weeks	0	2 (12.5)	0	2 (4.4)	2 (20.0)	4 (7.3)
> 48 - 60 weeks	1 (4.5)	2 (12.5)	1 (14.3)	4 (8.9)	1 (10.0)	5 (9.1)
> 60 - 72 weeks	1 (4.5)	5 (31.3)	3 (42.9)	9 (20.0)	0	9 (16.4)
> 72 - 84 weeks	3 (13.6)	2 (12.5)	0	5 (11.1)	1 (10.0)	6 (10.9)
> 84 - 96 weeks	3 (13.6)	0	0	3 (6.7)	0	3 (5.5)
> 96 - 120 weeks	3 (13.6)	1 (6.3)	0	4 (8.9)	1 (10.0)	5 (9.1)
> 120 - 144 weeks	0	0	0	0	1 (10.0)	1 (1.8)
> 144 weeks	0	0	0	0	2 (20.0)	2 (3.6)
Subject-Treatment-Years	21.2	15.9	5.3	42.3	14.9	57.3

Subject-Treatment-Years is the sum of each subject's treatment exposure in years. Source:

2.6.8.2. Adverse events

- Acute GvHD

In the pooled acute GvHD paediatric subjects, all 51 subjects had at least 1 AE, of which 45 subjects (88.2%) had an AE of grade ≥3. A total of 28 subjects (54.9%) had SAEs, of which 24 subjects (47.1%) had an SAE of grade ≥3. There were no fatal SAEs (Table 39).

- Chronic GvHD

For pooled chronic GvHD paediatric subjects, 53 subjects (96.4%) had at least 1 AE, of which 35 subjects (63.6%) had an AE of grade ≥3. A total of 31 subjects (56.4%) reported an SAE, of which 22 subjects (40.0%) had an SAE of grade ≥3. There were 3 subjects (5.5%) who experienced a fatal SAE (Table 40).

Table 39 Overview of adverse events in acute GvHD (Safety set)

	Study F12201								Study C2301		Studies F12201+C2301	
	≥12y-18y 10mg b.i.d.		≥6y-<12y 5mg b.i.d.		≥2y-<6y 4mg/m² b.i.d.		All subjects		≥12y-<18y 10mg b.i.d.		Total paediatric subjects	
	N=18		N=12		N=15		N=45		N=6		N=51	
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 (%)	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)	6 (100)	6 (100)	51 (100)	45 (88.2)
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)	4 (66.7)	4 (66.7)	27 (52.9)	22 (43.1)
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)	4 (66.7)	4 (66.7)	28 (54.9)	24 (47.1)
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)	3 (50.0)	3 (50.0)	10 (19.6)	9 (17.6)
Fatal SAEs	0	0	0	0	0	0	0	0	0	0	0	0
Treatment-related	0	0	0	0	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)	1 (16.7)	1 (16.7)	11 (21.6)	10 (19.6)
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)	1 (16.7)	1 (16.7)	9 (17.6)	8 (15.7)
AEs leading to dose reduction	8 (44.4)	8 (44.4)	4 (33.3)	3 (25.0)	6 (40.0)	6 (40.0)	18 (40.0)	17 (37.8)	1 (16.7)	0	19 (37.3)	17 (33.3)
AEs leading to dose interruption	6 (33.3)	5 (27.8)	3 (25.0)	2 (16.7)	3 (20.0)	3 (20.0)	12 (26.7)	10 (22.2)	1 (16.7)	1 (16.7)	13 (25.5)	11 (21.6)
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)	6 (100)	5 (83.3)	49 (96.1)	40 (78.4)

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 26.0, CTCAE version 4.03.

Table 40 Overview of adverse events in chronic GvHD (Safety set)

	Studies G12201								Study D2301		Studies G12201+D2301	
	≥12y - <18y 10 mg b.i.d.		≥6y - <12y 5mg b.i.d.		≥2y - <6y 4mg/m^2 b.i.d.		Al subjects		≥12y - <18y 10 mg b.i.d.		Total paediatric subjects	
	N=22		N=16		N=7		N=45		N=10		N=55	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse events	22 (100)	16 (72.7)	15 (93.8)	9 (56.3)	7 (100)	4 (57.1)	44 (97.8)	29 (64.4)	9 (90.0)	6 (60.0)	53 (96.4)	35 (63.6)
Treatment-related	16 (72.7)	11 (50.0)	6 (37.5)	4 (25.0)	4 (57.1)	1 (14.3)	26 (57.8)	16 (35.6)	2 (20.0)	1 (10.0)	28 (50.9)	17 (30.9)
SAEs	14 (63.6)	10 (45.5)	7 (43.8)	5 (31.3)	4 (57.1)	3 (42.9)	25 (55.6)	18 (40.0)	6 (60.0)	4 (40.0)	31 (56.4)	22 (40.0)
Treatment-related	7 (31.8)	7 (31.8)	1 (6.3)	0	0	0	8 (17.8)	7 (15.6)	1 (10.0)	1 (10.0)	9 (16.4)	8 (14.5)
Fatal SAEs	0	0	2 (12.5)	2 (12.5)	1 (14.3)	1 (14.3)	3 (6.7)	3 (6.7)	0	0	3 (5.5)	3 (5.5)
Treatment-related	0	0	0	0	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)	1 (10.0)	0	8 (14.5)	6 (10.9)
Treatment-related	2 (9.1)	2 (9.1)	1 (6.3)	0	0	0	3 (6.7)	2 (4.4)	0	0	3 (5.5)	2 (3.6)
AEs leading to dose reduction	5 (22.7)	4 (18.2)	1 (6.3)	1 (6.3)	1 (14.3)	1 (14.3)	7 (15.6)	6 (13.3)	1 (10.0)	0	8 (14.5)	6 (10.9)
AEs leading to dose interruption	5 (22.7)	4 (18.2)	2 (12.5)	2 (12.5)	1 (14.3)	1 (14.3)	8 (17.8)	7 (15.6)	3 (30.0)	2 (20.0)	11 (20.0)	9 (16.4)
AEs requiring additional therapy	20 (90.9)	12 (54.5)	14 (87.5)	9 (56.3)	7 (100)	4 (57.1)	41 (91.1)	25 (55.6)	8 (80.0)	6 (60.0)	49 (89.1)	31 (56.4)

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 26.0, CTCAE version 4.03.

Table 41 Adverse events by preferred term (> 10% overall) in acute GvHD (Safety set)

Preferred term	Study F12201								Study C2301		Studies F12201+C2301	
	≥12y - <18y 10mg b.i.d.		≥6y - <12y 5mg b.i.d.		≥2y - <6y 4mg/m^2 b.i.d.		All subjects		≥12y - <18y 10 mg b.i.d.		Total paediatric subjects	
	N=18		N=12		N=15		N=45		N=6		N=51	
	All Grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of subjects with at least one event	18 (100)	16 (88.9)	12 (100)	11 (91.7)	15 (100)	12 (80.0)	45 (100)	39 (86.7)	6 (100)	6 (100)	51 (100)	45 (88.2)
Anaemia	6 (33.3)	6 (33.3)	5 (41.7)	3 (25.0)	9 (60.0)	8 (53.3)	20 (44.4)	17 (37.8)	1 (16.7)	0	21 (41.2)	17 (33.3)
Neutrophil count decreased	5 (27.8)	5 (27.8)	2 (16.7)	1 (8.3)	5 (33.3)	4 (26.7)	12 (26.7)	10 (22.2)	0	0	12 (23.5)	10 (19.6)
Neutropenia	6 (33.3)	6 (33.3)	2 (16.7)	2 (16.7)	1 (6.7)	1 (6.7)	9 (20.0)	9 (20.0)	2 (33.3)	2 (33.3)	11 (21.6)	11 (21.6)
Pyrexia	3 (16.7)	0	3 (25.0)	0	4 (26.7)	0	10 (22.2)	0	1 (16.7)	0	11 (21.6)	0
Thrombocytopenia	7 (38.9)	7 (38.9)	0	0	2 (13.3)	2 (13.3)	9 (20.0)	9 (20.0)	2 (33.3)	2 (33.3)	11 (21.6)	11 (21.6)
Alanine aminotransferase increased	5 (27.8)	4 (22.2)	2 (16.7)	0	2 (13.3)	1 (6.7)	9 (20.0)	5 (11.1)	1 (16.7)	0	10 (19.6)	5 (9.8)
Hypertension	2 (11.1)	2 (11.1)	2 (16.7)	2 (16.7)	5 (33.3)	4 (26.7)	9 (20.0)	8 (17.8)	0	0	9 (17.6)	8 (15.7)
Hypokalaemia	4 (22.2)	3 (16.7)	3 (25.0)	1 (8.3)	0	0	7 (15.6)	4 (8.9)	1 (16.7)	1 (16.7)	8 (15.7)	5 (9.8)
Platelet count decreased	0	0	2 (16.7)	1 (8.3)	6 (40.0)	5 (33.3)	8 (17.8)	6 (13.3)	0	0	8 (15.7)	6 (11.8)
White blood cell count decreased	0	0	2 (16.7)	2 (16.7)	5 (33.3)	4 (26.7)	7 (15.6)	6 (13.3)	1 (16.7)	1 (16.7)	8 (15.7)	7 (13.7)
Abdominal pain	0	0	2 (16.7)	0	3 (20.0)	0	5 (11.1)	0	1 (16.7)	1 (16.7)	6 (11.8)	1 (2.0)
Cytomegalovirus infection reactivation	2 (11.1)	1 (5.6)	1 (8.3)	0	1 (6.7)	0	4 (8.9)	1 (2.2)	2 (33.3)	0	6 (11.8)	1 (2.0)
Cytomegalovirus test positive	1 (5.6)	0	1 (8.3)	0	4 (26.7)	0	6 (13.3)	0	0	0	6 (11.8)	0
Vomiting	1 (5.6)	1 (5.6)	1 (8.3)	0	2 (13.3)	1 (6.7)	4 (8.9)	2 (4.4)	2 (33.3)	0	6 (11.8)	2 (3.9)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade. MedDRA version 26.0, CTCAE version 4.03.

Table 42 Adverse events by preferred term (> 10% overall) in chronic GvHD (Safety set)

Preferred term	Study G12201								Study D2301		Studies G12201+D2301	
	≥12y - <18y 10mg b.i.d.		≥6y - <12y 5mg b.i.d.		≥2y - <6y 4mg/m^2 b.i.d.		All subjects		≥12y - <18y 10 mg b.i.d.		Total paediatric subjects	
	N=22		N=16		N=7		N=45		N=10		N=55	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Number of subjects with at least one event	22 (100)	16 (72.7)	15 (93.8)	9 (56.3)	7 (100)	4 (57.1)	44 (97.8)	29 (64.4)	9 (90.0)	6 (60.0)	53 (96.4)	35 (63.6)
COVID-19	4 (18.2)	2 (9.1)	2 (12.5)	0	2 (28.6)	0	8 (17.8)	2 (4.4)	3 (30.0)	0	11 (20.0)	2 (3.6)
Anaemia	6 (27.3)	6 (27.3)	2 (12.5)	2 (12.5)	2 (28.6)	1 (14.3)	10 (22.2)	9 (20.0)	0	0	10 (18.2)	9 (16.4)
Headache	5 (22.7)	0	2 (12.5)	0	0	0	7 (15.6)	0	3 (30.0)	1 (10.0)	10 (18.2)	1 (1.8)
Pyrexia	4 (18.2)	0	3 (18.8)	0	0	0	7 (15.6)	0	2 (20.0)	0	9 (16.4)	0
Hypertension	3 (13.6)	1 (4.5)	3 (18.8)	1 (6.3)	1 (14.3)	0	7 (15.6)	2 (4.4)	1 (10.0)	0	8 (14.5)	2 (3.6)
Neutrophil count decreased	5 (22.7)	5 (22.7)	2 (12.5)	2 (12.5)	1 (14.3)	1 (14.3)	8 (17.8)	8 (17.8)	0	0	8 (14.5)	8 (14.5)
Diarrhoea	2 (9.1)	0	2 (12.5)	0	1 (14.3)	0	5 (11.1)	0	2 (20.0)	0	7 (12.7)	0
Neutropenia	1 (4.5)	0	3 (18.8)	2 (12.5)	2 (28.6)	1 (14.3)	6 (13.3)	3 (6.7)	1 (10.0)	1 (10.0)	7 (12.7)	4 (7.3)
Platelet count decreased	5 (22.7)	4 (18.2)	2 (12.5)	2 (12.5)	0	0	7 (15.6)	6 (13.3)	0	0	7 (12.7)	6 (10.9)
Upper respiratory tract infection	1 (4.5)	0	2 (12.5)	0	2 (28.6)	0	5 (11.1)	0	2 (20.0)	1 (10.0)	7 (12.7)	1 (1.8)
Cough	2 (9.1)	0	2 (12.5)	0	0	0	4 (8.9)	0	2 (20.0)	0	6 (10.9)	0
Influenza	0	0	2 (12.5)	0	1 (14.3)	0	3 (6.7)	0	3 (30.0)	0	6 (10.9)	0
Pneumonia	3 (13.6)	1 (4.5)	2 (12.5)	1 (6.3)	0	0	5 (11.1)	2 (4.4)	1 (10.0)	0	6 (10.9)	2 (3.6)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade. MedDRA version 26.0, CTCAE version 4.03.

2.6.8.3. Serious adverse event/deaths/other significant events

2.6.8.3.1. Serious Adverse events

- **Acute GvHD**

In the pooled acute GvHD paediatric subjects overall, 28 subjects (54.9%) reported SAEs, of which 24 subjects (47.1%) reported SAEs of grade ≥3 (Table 43).

For the pooled acute GvHD paediatric subjects, there were no SAEs with fatal outcome.

- **Chronic GvHD**

For pooled chronic GvHD paediatric subjects, 31 subjects (56.4%) reported SAEs, of which 22 subjects (40.0%) reported SAEs of grade ≥3 (Table 42).

There were 3 SAEs with fatal outcomes that were recorded as on treatment deaths; none of which were suspected to be treatment related.

Table 43 Serious adverse events by preferred term in acute GvHD (Safety set)

	Study F12201								**Study C2301**		**Studies F12201+C2301**	
	≥12y - <18y 10mg b.i.d.		**≥6y - <12y 5mg b.i.d.**		**≥2y - <6y 4mg/m² b.i.d.**		**All subjects**		**≥12y - <18y 10 mg b.i.d.**		**Total paediatric subjects**	
	N=18		**N=12**		**N=15**		**N=45**		**N=6**		**N=51**	
Preferred term	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
Number of subjects with at least one event	11 61.1)	10 55.6)	7 (58.3)	6 (50.0)	6 (40.0)	4 (26.7)	24 53.3)	20 (44.4)	4 (66.7)	4 (66.7)	28 54.9)	24 47.1)
Pyrexia	1 (5.6)	0	1 (8.3)	0	2 (13.3)	0	4 (8.9)	0	0	0	4 (7.8)	0
Acute kidney injury	2 (11.1)	2 (11.1)	0	0	0	0	2 (4.4)	2 (4.4)	0	0	2 (3.9)	2 (3.9)
Febrile neutropenia	1 (5.6)	1 (5.6)	1 (8.3)	1 (8.3)	0	0	2 (4.4)	2 (4.4)	0	0	2 (3.9)	2 (3.9)
Hypokalaemia	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	1 (16.7)	1 (16.7)	2 (3.9)	2 (3.9)
Neutropenia	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	1 (16.7)	1 (16.7)	2 (3.9)	2 (3.9)
Sepsis	0	0	1 (8.3)	1 (8.3)	1 (6.7)	1 (6.7)	2 (4.4)	2 (4.4)	0	0	2 (3.9)	2 (3.9)
Septic shock	2 (11.1)	2 (11.1)	0	0	0	0	2 (4.4)	2 (4.4)	0	0	2 (3.9)	2 (3.9)

	Study F12201								Study C2301		Studies F12201+C2301	
	≥12y - <18y 10mg b.i.d. N=18		≥6y - <12y 5mg b.i.d. N=12		≥2y - <6y 4mg/m² b.i.d. N=15		All subjects N=45		≥12y - <18y 10 mg b.i.d. N=6		Total paediatric subjects N=51	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Thrombocytopenia	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	1 (16.7)	1 (16.7)	2 (3.9)	2 (3.9)
Viral haemorrhagic cystitis	1 (5.6)	1 (5.6)	0	0	1 (6.7)	0	2 (4.4)	1 (2.2)	0	0	2 (3.9)	1 (2.0)
White blood cell count decreased	0	0	1 (8.3)	1 (8.3)	0	0	1 (2.2)	1 (2.2)	1 (16.7)	1 (16.7)	2 (3.9)	2 (3.9)
Acidosis	0	0	0	0	1 (6.7)	1 (6.7)	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Adenovirus infection	0	0	1 (8.3)	1 (8.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Adenovirus test positive	1 (5.6)	0	0	0	0	0	1 (2.2)	0	0	0	1 (2.0)	0
Back pain	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Bone pain	0	0	0	0	0	0	0	0	1 (16.7)	1 (16.7)	1 (2.0)	1 (2.0)
Bronchitis	0	0	0	0	0	0	0	0	1 (16.7)	1 (16.7)	1 (2.0)	1 (2.0)
COVID-19	0	0	0	0	1 (6.7)	1 (6.7)	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Cough	0	0	0	0	0	0	0	0	1 (16.7)	1 (16.7)	1 (2.0)	1 (2.0)
Cytomegalovirus infection reactivation	0	0	0	0	0	0	0	0	1 (16.7)	0	1 (2.0)	0
Cytomegalovirus test positive	0	0	0	0	1 (6.7)	0	1 (2.2)	0	0	0	1 (2.0)	0
Cytomegalovirus viraemia	0	0	0	0	1 (6.7)	1 (6.7)	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Device related infection	0	0	1 (8.3)	1 (8.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Eye infection viral	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Gastric haemorrhage	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Gastroenteritis	0	0	0	0	1 (6.7)	1 (6.7)	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Graft versus host disease in gastrointestinal tract	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Haemorrhagic disorder	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Herpes zoster	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Intestinal haemorrhage	1 (5.6)	0	0	0	0	0	1 (2.2)	0	0	0	1 (2.0)	0
Intestinal perforation	0	0	1 (8.3)	1 (8.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Neutrophil count decreased	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Osteoporotic fracture	0	0	0	0	0	0	0	0	1 (16.7)	1 (16.7)	1 (2.0)	1 (2.0)
Pancreatitis acute	0	0	1 (8.3)	1 (8.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Pericardial effusion	0	0	1 (8.3)	1 (8.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Pneumonia	1 (5.6)	0	0	0	0	0	1 (2.2)	0	0	0	1 (2.0)	0

	Study F12201								Study C2301		Studies F12201+C2301	
	≥12y - <18y 10mg b.i.d. N=18		≥6y - <12y 5mg b.i.d. N=12		≥2y - <6y 4mg/m² b.i.d. N=15		All subjects N=45		≥12y - <18y 10 mg b.i.d. N=6		Total paediatric subjects N=51	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Posterior reversible encephalopathy syndrome	0	0	0	0	1 (6.7)	1 (6.7)	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Pulmonary embolism	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Renal failure	1 (5.6)	0	0	0	0	0	1 (2.2)	0	0	0	1 (2.0)	0
Respiratory failure	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Shock haemorrhagic	0	0	1 (8.3)	1 (8.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Skin infection	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Transaminases increased	0	0	0	0	0	0	0	0	1 (16.7)	1 (16.7)	1 (2.0)	1 (2.0)
Transplant dysfunction	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Upper respiratory tract inflammation	1 (5.6)	0	0	0	0	0	1 (2.2)	0	0	0	1 (2.0)	0

Numbers (n) represent counts of subjects.
AEs occurring during treatment or within 30 days of the last study medication are summarized.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 26.0, CTCAE version 4.03.

Table 44 Serious adverse events by preferred term in chronic GvHD (Safety set)

	Study G12201								Study D2301		Studies G12201+D2301	
	≥12y - <18y 10mg b.i.d. N=22		≥6y - <12y 5mg b.i.d. N=16		≥2y - <6y 4mg/m² b.i.d. N=7		All subjects N=45		≥12y - <18y 10 mg b.i.d. N=10		Total paediatric subjects N=55	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of subjects with at least one event	**.4 (63.6)**	**10 (45.5)**	7 (43.8)	5 (31.3)	4 (57.1)	3 (42.9)	25 (55.6)	18 (40.0)	6 (60.0)	4 (40.0)	31 (56.4)	22 (40.0)
Herpes zoster	2 (9.1)	2 (9.1)	0	0	0	0	2 (4.4)	2 (4.4)	1 (10.0)	1 (10.0)	3 (5.5)	3 (5.5)
Pyrexia	2 (9.1)	0	0	0	0	0	2 (4.4)	0	1 (10.0)	0	3 (5.5)	0
COVID-19	2 (9.1)	2 (9.1)	0	0	0	0	2 (4.4)	2 (4.4)	0	0	2 (3.6)	2 (3.6)
Hyponatraemia	2 (9.1)	2 (9.1)	0	0	0	0	2 (4.4)	2 (4.4)	0	0	2 (3.6)	2 (3.6)
Muscular weakness	2 (9.1)	0	0	0	0	0	2 (4.4)	0	0	0	2 (3.6)	0
Acute respiratory distress syndrome	0	0	1 (6.3)	1 (6.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Alveolar proteinosis	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Aspergillus infection	0	0	0	0	1 (14.3)	1 (14.3)	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Aura	1 (4.5)	0	0	0	0	0	1 (2.2)	0	0	0	1 (1.8)	0
Blood creatinine increased	0	0	1 (6.3)	0	0	0	1 (2.2)	0	0	0	1 (1.8)	0
Clostridium difficile infection	0	0	0	0	0	0	0	0	1 (10.0)	0	1 (1.8)	0
Dacryocanaliculitis	0	0	0	0	0	0	0	0	1 (10.0)	0	1 (1.8)	0
Decreased appetite	0	0	0	0	0	0	0	0	1 (10.0)	1 (10.0)	1 (1.8)	1 (1.8)
Dyspnoea	1 (4.5)	0	0	0	0	0	1 (2.2)	0	0	0	1 (1.8)	0
Epstein-Barr virus infection	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Febrile neutropenia	0	0	0	0	1 (14.3)	1 (14.3)	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Gastroenteritis viral	1 (4.5)	0	0	0	0	0	1 (2.2)	0	0	0	1 (1.8)	0
Hepatorenal syndrome	0	0	1 (6.3)	1 (6.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Human bocavirus infection	0	0	0	0	1 (14.3)	0	1 (2.2)	0	0	0	1 (1.8)	0
Infectious pleural effusion	0	0	1 (6.3)	1 (6.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Kaposi's sarcoma	0	0	0	0	0	0	0	0	1 (10.0)	0	1 (1.8)	0
Neutropenia	0	0	0	0	0	0	0	0	1 (10.0)	1 (10.0)	1 (1.8)	1 (1.8)
Oedema peripheral	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Pain in extremity	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)

	Study G12201								Study D2301		Studies G12201+D2301	
	≥12y - <18y 10mg b.i.d. N=22		≥6y - <12y 5mg b.i.d. N=16		≥2y - <6y 4mg/m² b.i.d. N=7		All subjects N=45		≥12y - <18y 10 mg b.i.d. N=10		Total paediatric subjects N=55	
Preferred term	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades n (%)	Grade ≥3 n (%)
Parainfluenzae virus infection	0	0	0	0	1 (14.3)	1 (14.3)	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Pneumatosis intestinalis	1 (4.5)	0	0	0	0	0	1 (2.2)	0	0	0	1 (1.8)	0
Pneumonia	0	0	1 (6.3)	1 (6.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Pneumonia fungal	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Pneumothorax	0	0	1 (6.3)	1 (6.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Post transplant lymphoproliferative disorder	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Presyncope	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Respiratory distress	0	0	1 (6.3)	1 (6.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Respiratory syncytial virus infection	0	0	1 (6.3)	0	0	0	1 (2.2)	0	0	0	1 (1.8)	0
Retinal vein occlusion	0	0	1 (6.3)	0	0	0	1 (2.2)	0	0	0	1 (1.8)	0
Sepsis	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Septic shock	0	0	1 (6.3)	1 (6.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Sinusitis	0	0	0	0	0	0	0	0	1 (10.0)	1 (10.0)	1 (1.8)	1 (1.8)
Steroid diabetes	1 (4.5)	0	0	0	0	0	1 (2.2)	0	0	0	1 (1.8)	0
Thrombocytopenia	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Tooth infection	0	0	0	0	1 (14.3)	1 (14.3)	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Transfusion related complication	0	0	1 (6.3)	1 (6.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Transplant failure	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Ulcerative keratitis	0	0	0	0	0	0	0	0	1 (10.0)	1 (10.0)	1 (1.8)	1 (1.8)
Urinary retention	1 (4.5)	0	0	0	0	0	1 (2.2)	0	0	0	1 (1.8)	0
Urinary tract infection	0	0	1 (6.3)	1 (6.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)

Numbers (n) represent counts of subjects.
AEs occurring during treatment or within 30 days of the last study medication are summarized.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 26.0, CTCAE version 4.03.

2.6.8.3.2. Deaths

- **Acute GvHD**

In the pooled acute GvHD paediatric subjects, a total of 13 deaths (25.5%) occurred, with 1 occurring while on-treatment due to disease progression in Study C2301 and 12 deaths during post-treatment, i.e., occurring more than 30 days after treatment discontinuation (Table 45). Out of the 9 post-treatment deaths, 6 subjects were from the SR-GvHD subgroup, as compared to 3 subjects in the treatment-naïve group.

Table 45 Overview of all deaths (on-treatment and post-treatment) in acute GvHD (Safety set)

Primary reason (preferred term)	Study F12201				Study C2301	Studies F12201+ C2301
	≥12y - <18y 10mg b.i.d. N=18 n (%)	≥6y - <12y 5mg b.i.d. N=12 n (%)	≥2y - <6y 4mg/m^2 b.i.d. N=15 n (%)	F12201 All subjects N=45 n (%)	≥12y - <18y 10 mg b.i.d. N=6 n (%)	Total paediatric subjects N=51 n (%)
Number of subjects who died	6 (33.3)	2 (16.7)	1 (6.7)	9 (20.0)	4 (66.7)	13 (25.5)
Study indication	2 (11.1)	0	0	2 (4.4)	1 (16.7)	3 (5.9)
Other	4 (22.2)	2 (16.7)	1 (6.7)	7 (15.6)	3 (50.0)	10 (19.6)
By preferred term						
Thrombotic microangiopathy	1 (5.6)	0	0	1 (2.2)	0	1 (2.0)
Disease progression	0	0	0	0	1 (16.7)	1 (2.0)
Acute graft versus host disease	2 (11.1)	0	0	2 (4.4)	1 (16.7)	3 (5.9)
Chronic graft versus host disease	1 (5.6)	0	0	1 (2.2)	0	1 (2.0)
Central nervous system fungal infection	0	0	0	0	1 (16.7)	1 (2.0)
Sepsis	1 (5.6)	0	0	1 (2.2)	0	1 (2.0)
Septic shock	1 (5.6)	0	0	1 (2.2)	0	1 (2.0)
Acute lymphocytic leukaemia recurrent	0	1 (8.3)	0	1 (2.2)	0	1 (2.0)
Acute myeloid leukaemia	0	1 (8.3)	0	1 (2.2)	0	1 (2.0)
Juvenile chronic myelomonocytic leukaemia	0	0	1 (6.7)	1 (2.2)	0	1 (2.0)
Respiratory failure	0	0	0	0	1 (16.7)	1 (2.0)

Numbers (n) represent counts of subjects.
All deaths occurring on-treatment or after 30 days of the last study medication are summarized. MedDRA version 26.0.

- **Chronic GvHD**

For pooled chronic GvHD paediatric subjects, a total of 10 deaths (18.2%) occurred, with 3 occurring on-treatment and 7 during post-treatment period, i.e., occurring more than 30 days after treatment discontinuation (Table 46). The three on-treatment deaths were reported due to acute respiratory distress syndrome, *Aspergillus* infection, and septic shock; none of which were suspected to be treatment-related. All 3 on-treatment deaths were from the SR-chronic GvHD subgroup; 2 of the 3 subjects had severe chronic GvHD and 1 subject had moderate chronic GvHD at baseline.

All 10 deaths occurred in Study G12201. Out of the 10 deaths, 9 subjects were from the SR-chronic GvHD subgroup and 1 subject from the treatment-naïve subgroup.

Table 46 Overview of all deaths (on-treatment and post-treatment) in chronic GvHD (Safety set)

Primary reason (preferred term)	Study G12201				Study D2301	Studies G12201+ D2301 Total paediatric subjects
	≥12y - <18y 10mg b.i.d.	≥6y - <12y 5mg b.i.d.	≥2y - <6y 4mg/m^2 b.i.d.	All subjects	≥12y - <18y 10 mg b.i.d.	
	N=22 n (%)	N=16 n (%)	N=7 n (%)	N=45 n (%)	N=10 n (%)	N=55 n (%)
Number of subjects who died	6 (27.3)	3 (18.8)	1 (14.3)	10 (22.2)	0	10 (18.2)
Study indication	0	0	0	0	0	0
Other	6 (27.3)	3 (18.8)	1 (14.3)	10 (22.2)	0	10 (18.2)
By preferred term						
Thrombotic microangiopathy	0	1 (6.3)	0	1 (2.2)	0	1 (1.8)
Cardiac arrest	1 (4.5)	0	0	1 (2.2)	0	1 (1.8)
Multiple organ dysfunction syndrome	1 (4.5)	0	0	1 (2.2)	0	1 (1.8)
Aspergillus infection	0	0	1 (14.3)	1 (2.2)	0	1 (1.8)
COVID-19	1 (4.5)	0	0	1 (2.2)	0	1 (1.8)
Pneumonia fungal	1 (4.5)	0	0	1 (2.2)	0	1 (1.8)
Septic shock	0	1 (6.3)	0	1 (2.2)	0	1 (1.8)
Transplant failure	1 (4.5)	0	0	1 (2.2)	0	1 (1.8)
Leukaemia recurrent	1 (4.5)	0	0	1 (2.2)	0	1 (1.8)
Acute respiratory distress syndrome	0	1 (6.3)	0	1 (2.2)	0	1 (1.8)

Numbers (n) represent counts of subjects.
All deaths occurring on-treatment or after 30 days of the last study medication are summarized. MedDRA version 26.0.

2.6.8.3.3. Other AEs of specific interest

Fractures

- Acute GvHD

One AEs of fracture (grade ≥3) was reported in patients with aGvHD in study C2301.

- Chronic GvHD

There were three AEs of fracture reported in patients with cGvHD: one event in study G12201 (in patients of ≥12-<18 group) and two events in study D2301.

2.6.8.4. Laboratory findings

Data from standard laboratory evaluations, i.e., haematology, biochemistry, and vital signs, were in line with the known safety profile of ruxolitinib and did not reveal any new safety concern.

2.6.8.4.1. Haematology

- **Acute GvHD**

At baseline, consistent with the study population disease characteristics, the majority of subjects with acute GvHD had low haemoglobin level (78.4%) and low platelet counts (72.5%); the majority of these laboratory abnormalities were CTC grade 1 or 2. Neutrophils counts were within normal limits for the majority of patients (82.4%). New or worsening to grade 3/4 abnormalities from baseline were

reported for haemoglobin decrease (grade 3: 22/48 subjects, 45.8%), platelet count decrease (grade 3: 6/41 subjects, 14.6%; grade 4: 11/49 subjects, 22.4%), and neutrophil decrease (grade 3: 16/50 subjects, 32.0%; grade 4: 11/50 subjects, 22.0%). When analysed by age group in Study F12201, worst post-baseline grade 3 haemoglobin decrease, and grade 3/4 platelets decreased was similar across age groups.

- **Chronic GvHD**

At baseline, patients with chronic GvHD had low haemoglobin level (47.2%), and low platelet counts (32.7%); the majority of these laboratory abnormalities were CTC grade 1 or 2. Neutrophils counts were within normal limits for the majority of patients (90.9%). New or worsening to grade 3/4 abnormalities from baseline were reported for haemoglobin decrease (grade 3: 9/53 subjects, 17.0%), platelet count decrease (grade 3: 4/52 subjects, 7.7%; grade 4: 6/54 subjects, 11.1%), and neutrophil count decrease (grade 3: 9/52 subjects, 17.3%; grade 4: 6/54 subjects, 11.1%). When analysed by age group in Study G12201, worst post-baseline grade 3 haemoglobin decrease, and grade 3/4 platelets decreased was similar across age groups except for lower proportions of grade 3 haemoglobin decrease noted in the ≥6 years to <12 years age group.

2.6.8.4.2. Clinical chemistry

- **Acute GvHD**

At baseline, elevated levels of alanine aminotransferase (49.0%), aspartate aminotransferase (33.3%), alkaline phosphatase (9.8%), bilirubin (17.6%), triglycerides (52.9%), cholesterol (17.6%), lipase (17.6%), amylase (17.6%) were reported. The majority of these laboratory abnormalities were CTC grade 1 or 2. Post-baseline, the majority of subjects had new or worsening grade 1 or 2 chemistry abnormalities with less subjects reporting grade 3 abnormalities. Grade 4 abnormalities were infrequently reported. Across age groups, few numerical differences were noted, however these differences should be interpreted with caution owing to the limited number of subjects across the age groups.

- **Chronic GvHD**

At baseline, elevated levels of alanine aminotransferase (38.2%), aspartate aminotransferase (38.2%), alkaline phosphatase (18.2%), bilirubin (9.1%), triglycerides (38.2%), cholesterol (36.4%), lipase (12.7%), amylase (7.3%) were reported. The majority of these laboratory abnormalities were CTC grade 1 or 2. Post-baseline, the majority of patients had new or worsening grade 1 or 2 chemistry abnormalities with less subjects reporting grade 3 abnormalities. Grade 4 abnormalities were infrequently reported. Across age groups, few numerical differences were noted however these differences should be interpreted with caution owing to the limited number of subjects across the age groups.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Subgroup analyses were conducted to identify potential safety issues restricted to certain subpopulations. Adverse events were evaluated for pre-specified subgroups including age, gender, race, region, and by baseline hepatic and renal impairment status.

The results from the subgroup analyses demonstrated a pattern of events in the subgroups that were consistent with that reported for the respective overall populations. Considering the differences in the number of patients between subgroups and duration of exposure to treatment, it is not appropriate to make a direct comparison and results need to be interpreted with caution. Within the ambit of these differences, the safety profile in subgroups was generally consistent with the respective overall population. No additional safety concerns were observed for subpopulations analysed.

Renal impairment

In acute and chronic GvHD studies, the vast majority of subjects had no baseline renal impairment. Based on exclusion criteria, subjects with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2 or renal dialysis requirement) at baseline were not enrolled. Hence, no clear conclusions could be made on the AE profile based on baseline renal impairment status.

Hepatic impairment

In acute and chronic GvHD studies, the vast majority of subjects had no hepatic impairment and therefore had small sample sizes in the other categories: mild, moderate, severe, and missing. Hence, no clear conclusions could be made on the AE profile based on hepatic impairment.

Growth and development and sexual maturation

The paediatric patients in clinical studies were also monitored for potential effects on growth and development (physical examination including routine monitoring of height and weight) and effects on puberty (Tanner staging). Overall, treatment of paediatric patients with ruxolitinib over time did not show any impact on gain in height, weight, or sexual maturation. It should be noted that the period of observation is not long enough to make any conclusions on the long-term growth and development of paediatric subjects.

2.6.8.7. Immunological events

Not applicable.

2.6.8.8. Safety related to drug-drug interactions and other interactions

No new safety concerns related to drug-drug interactions were identified in children with GvHD.

2.6.8.9. Discontinuation due to adverse events

Adverse events leading to discontinuation of study medicine are summarised in table 47 (for aGvHD) and table 48 (for cGvHD).

Dose interruption due to AEs

In the pooled acute GvHD paediatric subjects overall, 13 subjects (25.5%) required dose interruption due to AEs, of these 11 subjects (21.6%) had AEs of grade ≥3. Most AEs leading to interruption were reported for 1 subject each, apart from neutrophil count decreased reported in 4 subjects (7.8%) and neutropenia reported in 2 subjects (3.9%). A similar frequency of AEs leading to study treatment interruption was observed when Study F12201 was analysed by age group.

For pooled chronic GvHD paediatric subjects, 11 subjects (20.0%) required dose interruption due to AEs, of these 9 subjects (16.4%) had AEs of grade ≥ 3. Most AEs leading to interruption were reported for 1 subject each, apart from platelet count decreased reported in 2 subjects (3.6%). A similar

frequency of AEs leading to study treatment interruption was observed when Study G12201 was analysed by age group.

Adverse events leading to dose reduction

In the pooled acute GvHD paediatric subjects overall, 19 subjects (37.3%) required dose reduction due to AEs, of these 17 subjects (33.3%) had AEs of grade ≥ 3. Most AEs leading to dose reduction were reported for 1 subject each, apart from neutrophil count decreased (7 subjects, 13.7%), neutropenia (4 subjects, 7.8%), thrombocytopenia (3 subjects, 5.9%), and anaemia (2 subjects, 3.9%). A similar overall frequency of AEs leading to study treatment dose reduction was observed when analysed by age group in Study F12201.

For pooled chronic GvHD paediatric subjects, 8 subjects (14.5%) required dose reduction due to AEs, of these 6 subjects (10.9%) had AEs of grade ≥ 3. Most AEs leading to dose reduction were reported for 1 subject each, apart from neutropenia (2 subjects, 3.6%). A similar overall frequency of AEs leading to study treatment dose reduction was observed when Study G12201 was analysed by age group.

Table 47 Adverse events leading to study treatment discontinuation by system organ class and preferred term in acute GvHD (Safety set)

Category	Study F12201								Study C2301		Studies F12201+C2301	
	≥12y - <18y 10mg b.i.d.		≥6y - <12y 5mg b.i.d.		≥2y - <6y 4mg/m^2 b.i.d.		All subjects		≥12y - <18y 10 mg b.i.d.		Total paediatric subjects	
	N=18		N=12		N=15		N=45		N=6		N=51	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Number of subjects with at least one event	5 (27.8)	4 (22.2)	3 (25.0)	3 (25.0)	2 (13.3)	2 (13.3)	10 (22.2)	9 (20.0)	1 (16.7)	1 (16.7)	11 (21.6)	10 (19.6)
Blood and lymphatic system disorders	2 (11.1)	2 (11.1)	0	0	0	0	2 (4.4)	2 (4.4)	0	0	2 (3.9)	2 (3.9)
Neutropenia	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Thrombocytopenia	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Gastrointestinal disorders	0	0	1 (8.3)	1 (8.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Pancreatitis acute	0	0	1 (8.3)	1 (8.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Infections and infestations	0	0	1 (8.3)	1 (8.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Adenovirus infection	0	0	1 (8.3)	1 (8.3)	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Injury, poisoning and procedural complications	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Transplant dysfunction	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
Investigations	3 (16.7)	2 (11.1)	1 (8.3)	1 (8.3)	2 (13.3)	2 (13.3)	6 (13.3)	5 (11.1)	1 (16.7)	1 (16.7)	7 (13.7)	6 (11.8)
Neutrophil count decreased	0	0	1 (8.3)	1 (8.3)	1 (6.7)	1 (6.7)	2 (4.4)	2 (4.4)	0	0	2 (3.9)	2 (3.9)
Platelet count decreased	0	0	0	0	2 (13.3)	2 (13.3)	2 (4.4)	2 (4.4)	0	0	2 (3.9)	2 (3.9)
Transaminases increased	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	1 (16.7)	1 (16.7)	2 (3.9)	2 (3.9)
Alanine aminotransferase increased	1 (5.6)	0	0	0	0	0	1 (2.2)	0	0	0	1 (2.0)	0
Lipase increased	1 (5.6)	1 (5.6)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)
White blood cell count decreased	0	0	0	0	1 (6.7)	1 (6.7)	1 (2.2)	1 (2.2)	0	0	1 (2.0)	1 (2.0)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade. MedDRA version 26.0, CTCAE version 4.03.

Table 48 Adverse events leading to study treatment discontinuation by system organ class and preferred term in chronic GvHD (Safety set)

Category	Study G12201								Study D2301		Studies G12201+D2301	
	≥12y - <18y 10mg b.i.d.		≥6y - <12y 5mg b.i.d.		≥2y - <6y 4mg/m^2 b.i.d.		All subjects		≥12y - <18y 10 mg b.i.d.		Total paediatric subjects	
	N=22		N=16		N=7		N=45		N=10		N=55	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Number of subjects with at least one event	5 (22.7)	5 (22.7)	1 (6.3)	0	1 (14.3)	1 (14.3)	7 (15.6)	6 (13.3)	1 (10.0)	0	8 (14.5)	6 (10.9)
Blood and lymphatic system disorders	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Thrombocytopenia	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Eye disorders	0	0	1 (6.3)	0	0	0	1 (2.2)	0	0	0	1 (1.8)	0
Retinal vein occlusion	0	0	1 (6.3)	0	0	0	1 (2.2)	0	0	0	1 (1.8)	0
Infections and infestations	2 (9.1)	2 (9.1)	0	0	1 (14.3)	1 (14.3)	3 (6.7)	3 (6.7)	0	0	3 (5.5)	3 (5.5)
Aspergillus infection	0	0	0	0	1 (14.3)	1 (14.3)	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
COVID-19	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Herpes zoster	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Injury, poisoning and procedural complications	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Transplant dysfunction	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0	0	0	0	0	0	0	0	1 (10.0)	0	1 (1.8)	0
Kaposi's sarcoma	0	0	0	0	0	0	0	0	1 (10.0)	0	1 (1.8)	0
Respiratory, thoracic and mediastinal disorders	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)
Alveolar proteinosis	1 (4.5)	1 (4.5)	0	0	0	0	1 (2.2)	1 (2.2)	0	0	1 (1.8)	1 (1.8)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade. MedDRA version 26.0, CTCAE version 4.03.

2.6.8.10. Post marketing experience

The most recent PSUR for ruxolitinib covered the period from 23-Feb-2022 to 22-Feb-2023.

An estimate of patient exposure is calculated based on worldwide sales volume in kg of active substance sold and the recommended daily dose (30 mg). Up to the cut-off date of 22-Feb-2023, the cumulative patient exposure since the International Birth Date (16-Nov-2011) is estimated to be approximately 317,838 patient-treatment years.

Based on available data for post-marketing usage of ruxolitinib up to 22-Feb-2023, no new or changing safety signal has emerged that would substantially alter the known safety profile in the intended indication setting. There is no new or changing safety signal; the benefit/risk assessment was considered to remain favourable (and unchanged).

2.6.9. Discussion on clinical safety

The safety profile of ruxolitinib has been characterized in a clinical development program across several indications, including acute GvHD or chronic GvHD in patients aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies, and through an extensive post-approval experience.

The current application concerns an extension of indication for the use of ruxolitinib in paediatric patients aged 28 days or older with acute or chronic GvHD.

The safety data set includes all patients who received at least one dose of study medicine in studies F12201 and G12201, as well as paediatric patients from the studies C2301 and D2301. The safety data set in acute GvHD and chronic GvHD includes 51 and 56 subjects from ≥2 to <18 years, respectively. There was no subject younger than 2 years enrolled to the studies.

The main studies F12201 and G12201 were open-label, uncontrolled and single arm. Absence of control group and number of confounders, e.g., GvHD itself, concomitant treatment with other immunosuppressants, preclude thorough assessment of safety related to ruxolitinib. Due to difference in study population in acute and chronic GvHD, discussion on safety in these groups is presented separately.

<u>Acute GvHD</u>

The planned duration of treatment for aGvHD was 24 weeks with possibility to continue to taper beyond 24 weeks. The median time of exposure for pooled acute GvHD paediatric subjects was 16.7 weeks (range: 1.1-48.9 weeks).

The considerably lower median exposure was in children of ≥12y to <18y age group (11.6 weeks) compared to younger children: 20.0 and 17.6 weeks in the ≥2y to <6y group and ≥6y to <12y groups, respectively. The median exposure was slightly longer in corticosteroid-refractory acute GvHD subjects (127.5 days) than in treatment-naïve subjects (111 days).

All 51 patients with aGvHD experienced at least one AE during the study. Slightly more than half of subject (28; 54.9%) had serious AEs. There was no serious AE with fatal outcome. In 11 patients, AEs (9 treatment related) lead to treatment discontinuation. Of note, treatment was discontinued twice as often in older patient groups compared to the group from 2 to 6 years. Dose was reduced or interrupted due to AEs in 19 and 13 subjects, respectively. Treatment related AEs were slightly less frequent in the youngest patients compared to older groups. Due to the small number of patients in

different age groups, the identified numerical difference in AEs is difficult to interpret; however, the lower observed exposure to ruxolitinib in patients from 2 to 6 years may play a role.

The most commonly reported AEs were from the SOCs Infections and infestations, Blood and lymphatic system disorders and Investigations. The most commonly reported PTs were those related to blood dyscrasias (anaemia, neutropenia, thrombocytopaenia) and to infections. These AEs are expected knowing the established safety profile of ruxolitinib.

Half of subjects reported serious AEs. Most of them were related to blood dyscrasias and infections. Serious AEs were reported more frequently in older children and in those with SR aGvHD.

A total of 13 deaths occurred in aGvHD patients. Only one death was reported while on-treatment due to disease progression, the remaining of deaths occurred more than 30 days after treatment discontinuation. The primary causes of deaths were aGvHD, infections and neoplasms. The fatal outcome occurred twice as common in subjects with SR aGvHD compared to treatment-naïve aGvHD (6 vs. 3).

Data from standard laboratory evaluations, i.e., haematology, biochemistry, and vital signs, were in line with the known safety profile of ruxolitinib and did not reveal any new safety concern.

Chronic GvHD

The planned duration of treatment for chronic GvHD (Studies D2301 and G12201) was 36 months. The median time of exposure for pooled chronic GvHD paediatric subjects was 57.1 weeks (range: 2.1-155.4 weeks).

The lower median exposure was in children of ≥12y to <18y age group (41.5 weeks) compared to younger children: 58.9 and 59.1 weeks in the ≥2y to <6y group and ≥6y to <12y groups, respectively. The median exposure was longer in treatment naïve subjects (61.9 weeks) than in SR-chronic GvHD subjects (50.4 weeks). The current patient exposure is insufficient to assess the long-term safety of the product in paediatric patients with cGvHD. Having considered this, 'Long term safety in paediatric patients with GvHD' is included to the RMP as missing information which is going to be further evaluated in ongoing study G12201 (additional pharmacovigilance).

53 patients out of 55 with cGvHD experienced at least one AEs during the study, 35 (63,6%) subjects experienced grade ≥3 AEs, around half of them were assesses as treatment related.

More than half of subjects (31; 56.4%) had serious AEs, of which only 9 were assessed as treatment related. There was 3 serious AEs with fatal outcome. None of them was assessed as treatment related. In 8 patients AEs (3 treatment related) lead to treatment discontinuation. Dose was reduced or interrupted due to AEs in 8 and 11 subjects, respectively.

AE's deemed treatment related were more frequent in the oldest patients compared to the younger ones. Due to the small number of patients in different age groups, the identified numerical difference in AEs is difficult to interpret; however, the lower observed exposure to ruxolitinib in patients from 2 to 6 years may play a role.

The most commonly reported AEs were from the SOCs Infections and infestations, Investigations and Blood and lymphatic system disorders. The most commonly reported PTs were those related to blood dyscrasias (anaemia, neutropenia, thrombocytopaenia) and to infections (COVID-19, pneumonia, pyrexia), which are expected based on the established safety profile of ruxolitinib. No new safety concerns have been identified.

More than half of subjects reported serious AEs, majority of them were grade ≥3. The most frequently reported AEs were herpes zoster, pyrexia. Serious AEs were numerically more frequent in older

patients and in those with SR aGvHD. In general, SAEs are in line with the known safety profile of ruxolitinib.

A total of 10 deaths occurred in cGvHD patients, all in the study G12201. Three deaths occurred while on-treatment, and seven deaths occurred more than 30 days after treatment discontinuation. The primary cause of deaths was infections (4 subjects). The fatal outcome occurred in 9 subjects with SR cGvHD compared to 1 in treatment-naïve cGvHD.

The adverse events of special interest were identified based on the known safety profile of ruxolitinib. They included infections excluding tuberculosis, leukopenia, bleeding (haemorrhage), elevated transaminases. There were no unexpected patterns regarding the AESI identified in the acute or chronic GvHD patients. There were no unexpected findings related to laboratory values or vital signs.

Fractures have been reported in one patient with aGvHD and in three patients with cGvHD. Three of these patients were treated with ruxolitinib, the remaining patient received BAT. The age of patients was 13, 33, 16,5 and 73 years. All these patients have had confounding factors, including long-term treatment with steroids, steroid diabetes, osteonecrosis, osteoporosis. Time to onset in the ruxolitinib cases was 21, 25 and 64 days. Having considered confounding factors, short TTO, the causal association between fractures and ruxolitinib is doubtful.

The choice of ADRs included in the SmPC was based on experience from the previous phase 3 studies (C2301 and D2301). No new ADRs were identified in studies F12201 and G12201.

In the response to questions on considerably lower exposure to ruxolitinib in younger patients, the applicant proposed the following changes to the dosage regimen: aGvHD - in children 28 days to <2 years the dose is increased from 4 mg/m^2 BID to 8 mg/m^2 BID; cGvHD - in children from 2 to <6 years the dose is increased from 4 mg/m^2 BID to 8 mg/m^2 BID and in children 6 months to <2 years the dose is increased from 4 mg/m^2 BID to 8 mg/m^2 BID (see Discussion on Clinical Pharmacology section). These newly proposed dosage regimen may result in increased toxicity in younger children. However, these ADRs are manageable, and significant alteration of safety profile is not expected given the extent of different exposure.

2.6.10. Conclusions on the clinical safety

The overall safety profile of ruxolitinib in paediatric patients with both acute and chronic GvHD is consistent with its established safety profile and as expected in the study population. The safety profile of ruxolitinib is mainly characterised by cytopenias and infections which appears to be manageable with the dose modification and appropriate treatment. No new safety concerns were identified in the paediatric GvHD studies with ruxolitinib therapy.

However, there was no subject younger than 2 years enrolled to the studies, thus the safety in children ≥28 days - <2 years has not been evaluated. Although no safety signal has been identified in paediatric patients in clinical trials, the potential of developmental toxicity in young children cannot be ruled out. Therefore, developmental toxicity is included to the RMP as important potential risk. In addition, it is recommended to monitor and assess the safety in children ≥28 days - <2 years within PSURs.

Long term safety in paediatric patients is included as missing information to the RMP and will be further assessed within ongoing study G12201 which is added to the RMP as additional pharmacovigilance activity.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 49: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Serious infections
Important potential risks	Developmental toxicity
Missing information	Long-term safety in paediatric patients (GvHD only)

2.7.2. Pharmacovigilance plan

Table 50: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Interventional study Study INC424G12201 Ongoing	To evaluate the activity of ruxolitinib added to standard dose corticosteroids, ± CNI, in paediatric subjects with moderate or severe treatment naive-cGvHD or SR cGvHD	Long-term safety in paediatric patients (GvHD only)	Date of initiation Final CSR	May-2020 31-Dec-2025

2.7.3. Risk minimisation measures

Table 51: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Important identified risk	
Serious infections	**Routine risk communication** SmPC Section 4.4 SmPC Section 4.8 **Routine risk minimization activities recommending specific clinical measures:** Patients should be assessed for the risk of developing serious infections. Treatment with ruxolitinib should not be started until active serious infections have resolved. **Other routine risk minimization measures beyond the Product Information:** None

Important potential risk	
Developmental toxicity	**Routine risk communication** SmPC Section 4.1 SmPC Section 4.2 SmPC Section 4.3 SmPC Section 4.6 SmPC Section 5.3 **Routine risk minimization activities recommending specific clinical measures:** Women of childbearing potential should use effective contraception during the treatment. Should pregnancy occur during treatment with ruxolitinib, a risk/benefit evaluation must be carried out on an individual basis with careful counselling regarding potential risks to the fetus. Breastfeeding should be discontinued when treatment with ruxolitinib is started. **Other routine risk minimization measures beyond the Product Information:** None
Missing information	
Long-term safety in paediatric patients (GvHD only)	**Routine risk communication** SmPC Section 4.2 **Routine risk minimization activities recommending specific clinical measures:** None **Other routine risk minimization measures beyond the Product Information:** None

No additional risk minimization measures are proposed.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 16.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

- *Acute GvHD:*

  treatment of adults and paediatric patients aged 28 days and older with acute graft versus host disease who have inadequate response to corticosteroids or other systemic therapies.

- *Chronic GvHD*

  treatment of adults and paediatric patients aged 6 months and older with chronic graft versus host disease who have inadequate response to corticosteroids or other systemic therapies.

3.1.2. Available therapies and unmet medical need

The optimal practice for paediatric GvHD prophylaxis and treatment is not clearly defined and varies across institutions, but corticosteroids are almost universally used in first-line treatment for acute and chronic GvHD in adult and paediatric patients.

Corticosteroids have detrimental effects in children such as fluid retention, insulin resistance, proximal myopathy, hypertension, skin atrophy, bone resorption, femoral head avascular necrosis, and immunosuppression.

GvHD prophylaxis is often based on immunosuppression regimens such as a Calcineurin inhibitor (CNI, cyclosporine A or tacrolimus) with or without a short course of methotrexate. Treatments vary across institutions.

3.1.2.1. Acute GvHD

Corticosteroids are the mainstay of aGvHD therapy, with a high inter-center variability in the starting dose of corticosteroids.

Although details and definitions of corticosteroid refractoriness vary considerably, about one third to half of paediatric patients with aGvHD do not respond to upfront corticosteroid therapy. Second-line therapies are often considered if there is no response to corticosteroids after 2-7 days or if there is rapid progression within 48-72 h. There is no consensus on the choice of optimal second-line therapy for paediatric aGvHD.

aGvHD is one of the leading causes of mortality post alloHSCT. The non-relapse mortality (NRM) has been reported to be 26% for grade III and 68% for grade IV aGvHD (Zecca et al 2018). Adult and paediatric patients with grade III-IV aGvHD have a high mortality risk with a 2-year survival rate of 27-35% (Khoury et al 2017).

Except for ruxolitinib, currently approved for the treatment of acute or chronic GvHD in adolescent patients 12 to <18 years with inadequate response to corticosteroids or other systemic therapies, there are no treatments approved in the EU for use in paediatric aGvHD.

In the US, ruxolitinib is approved for the treatment of adult and paediatric patients 12 years and older with steroid-refractory (SR)-aGvHD.

3.1.2.2. Chronic GvHD

Systemic therapy is warranted in patients with moderate to severe cGvHD. Corticosteroids with or without a CNI is the standard of care in first line irrespective of the age. Steroid-free practice is typically applied to less than 20% of patients with certain comorbidities and previous complications of HSCT (Moiseev et al 2020, Moiseev et al 2023).

About 50% to 60% of paediatric patients develop corticosteroid-refractory or corticosteroid-dependent disease and require addition of another systemic therapy beyond systemic corticosteroids and CNIs within 2 years after initial therapy. No standard therapy has been established for SR patients and a range of agents have been used off-label.

Moderate to severe chronic GvHD is the major cause of transplant-related mortality and inferior OS following alloHSCT. Children with severe chronic GvHD experience a 10-year non-relapse mortality rate of about 35%, compared with 4-5% among children with mild to moderate chronic GvHD (Inagaki et al 2015).

In addition, cGvHD adversely affects physical and functional well-being as well as quality of life of most of the patients who are otherwise cured for their underlying disease after HSCT.

Except for ruxolitinib, currently approved for the treatment of acute or chronic GvHD in adolescent patients 12 to <18 years with inadequate response to corticosteroids or other systemic therapies, there are no treatments approved in the EU for use in paediatric cGvHD.

In the US, ruxolitinib is approved for cGvHD after failure of one or two lines of systemic therapy in adult and paediatric patients 12 years and older.

3.1.3. Main clinical studies

The MAH provided two pivotal paediatric single-arm studies to support the two claimed indications:

- Study **F12201/REACH4** was a Phase I/II open-label, single-arm, multi-center study of ruxolitinib added to corticosteroids in paediatric subjects with grade II-IV **acute GvHD** after alloHSCT. The purpose of the study was to assess safety, efficacy, and pharmacokinetics of ruxolitinib treatment with corticosteroids in treatment-naïve and steroid refractory (SR)-acute GvHD subjects aged ≥ 28 days to <18 years of age.
- Study **G12201/REACH5** was an open-label, single-arm, Phase II multi-center study of ruxolitinib added to immunosuppressive treatment in paediatric subjects with moderate or severe **chronic GvHD** after alloHSCT. The purpose of the study was to assess the pharmacokinetics (PK), safety and activity of ruxolitinib in treatment-naive or corticosteroid-refractory (SR)-chronic GvHD) subjects aged ≥ 28 days to <18 years.

In study **F12201**, the primary endpoint was ORR (complete response and partial response) at day 28 according to standard criteria by Harris et al 2016. Complete response was defined as complete resolution of all signs of aGvHD in all evaluable organs. Partial response was defined as improvement of 1 stage in 1 or more involved organs without progression in other sites.

In study **G12201**, the primary endpoint was ORR (complete response and partial response) at cycle 7 day 1 according to 2014 NIH Recommendations by Jagasia et al 2015. Complete response was defined as complete resolution of all signs of cGvHD in all evaluable organs. Partial response was defined as an improvement of GvHD in at least one organ without progression in other sites.

3.2. Favourable effects

Acute GvHD study F12201

The primary endpoint ORR at Day 28 (all patients, n=45) was 84% (90%CI: 73, 93), with CR reported in 49% of subjects. For SR subjects included in the indication (n=32), ORR at day 28 was 91% (90% CI: 78, 97).

Chronic GvHD study G12201

The primary endpoint ORR at Cycle 7 Day 1 (all patients, n=45) was 40% (90%CI: 28, 53).

For SR subjects included in the indication (n=28), ORR at Cycle 7 Day 1 was 39% (90% CI: 24, 57).

Extrapolation of efficacy by PK bridging

Extrapolation of efficacy from adults to paediatric patients to support dosing recommendation in paediatric patients should be based on the principle of exposure matching (Day 1 $AUC_{0\text{-}12h}$). The predicted mean Day 1 $AUC_{0\text{-}12h}$ for study F12201 were 274 ng/mL.h (2 to <6 years), 354 ng/mL.h (6 to <12 years), and 646 ng/mL.h (12 to <18 years). For study G12201 the predicted mean Day 1 $AUC_{0\text{-}12h}$ were 204 ng/mL.h (2 to <6 years), 497 ng/mL.h (6 to <12 years), and 633 ng/mL.h (12 to <18 years). The target exposure in the adult population was defined as 539 ng/mL.h. The revised posology (5 mg twice daily for patients 6 years old to less than 12 years old and 8 mg/m^2 twice daily for patients less than 6 years old) provides similar exposure of the paediatric population and the adult reference population.

3.3. Uncertainties and limitations about favourable effects

Given the add-on design in these two single-arm trials, it cannot be ascertained to what extent the objective responses that were recorded in SR and treatment-naïve aGvHD/study F12201 and cGvHD/study G12201, were due to the efficacy of ruxolitinib.

The uncertainty regarding the model performance is high and cannot be verified in the age group of interest as no clinical data is available, thus the uncertainty regarding the model predicted exposure is high and cannot be verified in the age group of interest.

3.4. Unfavourable effects

The safety profile of ruxolitinib has been characterised in clinical trial programme and post-marketing setting in several indications including acute or chronic GvHD in patients inadequately controlled with corticosteroids or other treatment in patients older than 12 years. Thus, the safety in the applied indication may be compared to the already known safety profile. This includes e.g., myelosuppression, consequent infections (including opportunists) and bleeding, as well as hepatotoxicity.

AEs were reported in all but two patients, and treatment related AEs were reported in half of study population both in aGVH and cGvH disease. Serious AEs were reported in 54.9% and 56.4% of patients with aGvHD and cGvHD respectively. Of these, 19.6% and 16.4%, respectively, were assessed by the investigator as treatment related.

AEs grade ≥3 were reported in 88.2% (43.1% treatment related) in aGvHD and in 63.6% (30.9% treatment related) in cGvHD.

SAEs with fatal outcome reported in three subjects with cGvHD, none was treatment related.

The most commonly reported AEs in were from the SOCs Infections and infestations, Blood and lymphatic system disorders and Investigations. The most frequent AEs reported in patients with aGvHD were anaemia (41.2%; grade ≥3 – 33.3%), neutrophil count decreased (23.5%; grade ≥3 – 19.6%), neutropenia (21.6%; grade ≥3 – 21.6%), pyrexia (21.6%), thrombocytopenia (21.6%; grade ≥3 – 21.6%).

The most frequent AEs reported in patients with cGvHD were COVID-19 (20%; grade ≥3 – 3.6%) anaemia (18.2%; grade ≥3 – 16.4%), headache (18.2%; grade ≥3 – 1.8%), pyrexia (16.4%), hypertension (14.5%; grade ≥3 – 3.6%); neutrophil count decreased (14.5%; grade ≥3 – 14.5%).

Serious AEs reported in more than one patient with aGvHD were pyrexia (4), acute kidney injury, febrile neutropenia, hypokalaemia, neutropenia, sepsis, septic shock, thrombocytopenia, viral haemorrhagic cystitis and white blood cell count decreased (two of each). SAEs related to treatment and reported more than in one patient with aGvHD were neutropenia and white blood cell count decreased.

Serious AEs reported in more than one patient with cGvHD were herpes zoster (3), pyrexia (3), COVID-19, hyponatraemia, muscular weakness (two of each). SAEs related to treatment and reported more than in one patient with cGvHD were herpes zoster and hyponatraemia.

AEs leading to discontinuation of treatment identified in 21.6% (17.6% treatment related) and 14.5% of patients with aGvHD and cGvHD respectively.

AEs leading to dose reduction reported in 37.3% and 14.5% of patients with aGvHD and cGvHD respectively.

AEs leading to dose interruption reported in 25.5% and 20% of patients with aGvHD and cGvHD respectively.

Numerical difference in AEs was observed between age subgroups. Treatment related SAEs were more frequent in the oldest patients compared to the younger ones. However, the small number of patients in different age groups precludes interpretation of these findings. The lower observed exposure to ruxolitinib in patients from 2 to 6 years may play a role.

3.5. Uncertainties and limitations about unfavourable effects

The single arm uncontrolled design of the studies in paediatric patients (F12201 and G12201), small number of patients in different age groups an add-on ruxolitinib treatment limits the interpretation of safety findings.

The further uncertainty is related to lower observed exposure to ruxolitinib in the ≥2-<6 age group which might result in a lower adverse effect burden. In the response to questions on the lower exposure to ruxolitinib in younger patients, the MAH proposed the following changes to the dosage regimen: aGvHD - in children 28 days to <2 years the dose is increased from 4 mg/m^2 BID to 8 mg/m^2 BID; cGvHD - in children from 2 to <6 years the dose is increased from 4 mg/m^2 BID to 8 mg/m^2 BID and in children 6 months to <2 years the dose is increased from 4 mg/m^2 BID to 8 mg/m^2 BID. These newly proposed dosage regimen may result in increased toxicity in younger children. However, these ADRs are manageable, and significant alteration of safety profile is not expected given the extent of different exposure.

Patients younger than 2 years were not enrolled to the study. Thus, the safety in age group from ≥28 days to <2 years has not been evaluated. Although no safety signal has been identified in paediatric patients in clinical trials, the potential of developmental toxicity in young children cannot be ruled out. Based on this data, developmental toxicity is included to the RMP as important potential risk. In addition, it is recommended to monitor and assess the safety for this patient group within PSURs.

Long term safety in paediatric patients is also unknow. This safety concern is included to the RMP as missing information and is going to be evaluated using additional pharmacovigilance activities.

3.6. Effects Table

Table 52. Effects Table for Jakavi on acute GvHD (study F12201, data cut-off: 02-Feb-2023) and Jakavi on Chronic GvHD (study G12201, data cut-off: 19-Oct-2022)

Effect	Short Description	Unit	Treatment	Control	Uncertainties	
Favourable Effects study F12201 acute GvHD DCO 02-Feb-2023, Final analysis						
ORR at day 28 (primary endpoint)	Overall response rate ORR (CR+PR)	%	84 90% CI (73, 93)	NA	Exploratory, single-arm trial, limited sample size Add-on design, ruxolitinib effect cannot be isolated 90% CI	
ORR at day 56 (key secondary endpoint)	Overall response rate ORR (CR+PR)	%	67 (90% CI 53, 78)	NA		
Favourable Effects study G12201 chronic GvHD DCO 19-Oct-2022, Interim analysis						
ORR at Cycle 7 day 1 (primary endpoint)	Overall response rate ORR (CR+PR)	%	40 (90% CI: 28, 53)		Exploratory, single-arm trial, limited sample size. Add-on design, ruxolitinib effect cannot be isolated 90% CI	

Effect	Short Description	Unit	Treatment	Control	Uncertainties
Unfavourable Effects					
aGvHD					The main studies were single arm uncontrolled. Ruxolitinib was used as add-on treatment. It is difficult to differentiate AEs related to ruxolitinib from those caused by the indication itself and/or concomitant treatment. Despite this, the safety in paediatric patients with acute or chronic GvHD looks similar to the known safety profile of ruxolitinib.
Anaemia	All grades	%	41.2	NA	
	Grade ≥3	%	33.3	NA	
Neutrophil count decrease	All grades	%	23.5	NA	
	Grade ≥3	%	19.6	NA	
Neutropenia	All grades	%	21.6	NA	
	Grade ≥3	%	21.6	NA	
Pyrexia	All grades	%	21.6	NA	
Thrombocytopenia	All grades	%	21.6	NA	
	Grade ≥3	%	21.6	NA	
cGvHD					
COVID-19	All grades	%	20.0	NA	
	Grade ≥3	%	3.6	NA	
Anaemia	All grades	%	18.2	NA	
	Grade ≥3	%	16.4	NA	
Headache	All grades	%	18.2	NA	
	Grade ≥3	%	1.8	NA	
Pyrexia	All grades	%	16.4	NA	
Hypertension	All grades	%	14.5	NA	
	Grade ≥3	%	3.6	NA	
Neutrophil count decreased	All grades	%	14.5	NA	
	Grade ≥3	%	14.5	NA	

Abbreviations: NA – not applicable

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The present application concerns both acute and chronic GvHD in steroid refractory (SR) paediatric subjects.

The previously approved indication in GvHD for Jakavi includes patients above 12 years of age with steroid refractory acute or chronic GvHD.

There is biological rationale for a benefit of ruxolitinib in paediatric patients < 12 years of age with acute or chronic GvHD in both in SR and treatment-naïve setting. Moreover, steroid sparing is a valid treatment goal, given the toxicity of corticosteroids.

Extrapolation from adults to children of the efficacy of a targeted immunomodulator for the treatment of acute and chronic GVHD by matching exposure is acceptable. The cause of these diseases is the same in adults and children, as are the disease manifestations. The present treatment paradigm, including e.g., steroids and calcineurin inhibitors, is the same, and treatment responses are not qualitatively different. The mode of action of ruxolitinib is anticipated to be similar regardless of age. Moreover, this extrapolation has already been accepted for Jakavi from adults to adolescents. With respect to clinical safety, the adverse events profile seen in uncontrolled paediatric studies is qualitatively similar to that seen in adults.

In summary, there is a rationale for extrapolation of adult data to children based on disease manifestation, mode of action, non-clinical data, PK data and (expected) clinical efficacy and safety.

In general, the MAH has established a PK bridge to the previous adult efficacy demonstration of ruxolitinib in SR aGvHD (REACH2/C2301) and SR cGvHD (REACH3/D2301), since the revised posology display similar exposure, in all paediatric age groups, as observed in the adult studies.

Since study F12201 and G12201 were not designed to isolate the effect of ruxolitinib, the MAH's claims ultimately rest on this establishment of a PK bridge to the adult efficacy demonstration in SR acute and chronic GvHD.

3.7.2. Balance of benefits and risks

Efficacy for the proposed use in SR acute and chronic GvHD has been established based on PK bridging to adult use. The safety profile is acceptable.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Jakavi in the treatment of:

- paediatric patients aged 28 days and older with acute graft versus host disease who have inadequate response to corticosteroids or other systemic therapies and

- paediatric patients aged 6 months and older with chronic graft versus host disease who have inadequate response to corticosteroids or other systemic therapies

is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Jakavi 5 mg/ml oral solution is favourable in the following indications:

Graft versus host disease (GvHD)

Acute GvHD
Jakavi is indicated for the treatment of adults and paediatric patients aged 28 days and older 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 adults and paediatric patients aged 6 months and older with chronic graft versus host disease who have inadequate response to corticosteroids or other systemic therapies (see section 5.1).

In addition, the CHMP considers by consensus that the benefit-risk balance of the existing 5 mg, 10 mg, 15 mg and 20 mg tablet formulation is favourable in 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 adults and paediatric patients aged 28 days and older 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 adults and paediatric patients aged 6 months and older with chronic graft versus host disease who have inadequate response to corticosteroids or other systemic therapies (see section 5.1).

The CHMP therefore recommends the extension of the marketing authorisation for Jakavi subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plans P/0527/2021 and P/0172/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.