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Human Medicines Division

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

Jakavi

ruxolitinib

Procedure no: EMEA/H/C/002464/P46/018

Note

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

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Table of contents

1. Introduction

On 5-10-2021, the MAH submitted a completed paediatric study for ruxolitinib, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

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

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

This phase III randomized open-label multicentre study of ruxolitinib versus best available therapy in patients with corticosteroid-refractory acute graft vs. host disease after allogeneic stem cell transplantation (CINC424C2301) is a stand-alone study and is part of a paediatric clinical development program.

With this submission related to Art 46, no changes to the paediatric information of the current Jakavi company Core Data Sheet or the current EU SmPC are proposed as a result of Study C2301.

2.2. Information on the pharmaceutical formulation used in the study

Ruxolitinib tablets have been developed as immediate release uncoated tablets of 5 mg, 10 mg, 15 mg, 20 mg and 25 mg strengths for oral administration. The higher strengths are quantitatively and qualitatively proportional to the 5 mg tablet.

In clinical studies with GvHD, only 5 mg tablets were used to allow for dose adjustments.

Ruxolitinib 10 mg b.i.d. (2x 5 mg tablets b.i.d) was the dose used in study C2301 in adolescents and adults.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for the study CINC424C2301: a phase III randomized open-label multi-center study of ruxolitinib versus best available therapy in patients with corticosteroid-refractory acute graft vs. host disease after allogeneic stem cell transplantation (hereafter referred to as study C2301).

2.3.2. Clinical study

A Phase III randomized open-label multi-center study of ruxolitinib versus best available therapy in patients with corticosteroid-refractory acute graft vs. host disease after allogeneic stem cell transplantation (CINC424C2301)

Description

This Phase III randomized study, C2301, was conducted to investigate the efficacy and safety of ruxolitinib versus investigator-choice BAT added to the patient's immunosuppression regimen in adults and adolescents ≥12 years old with Grade II-IV SR-aGvHD.

Methods

Objective(s)

Primary objective

- To compare the efficacy of ruxolitinib vs. Investigator's choice Best Available Therapy (BAT) in patients with Grade II-IV Steroid Refractory (SR)-aGvHD assessed by Overall Response Rate (ORR) at Day 28

Key secondary objective

- To compare the rate of durable ORR at Day 56 between ruxolitinib and BAT

The primary and key secondary objectives were analysed and presented in the Primary Analysis CSR. The analyses of the primary and key secondary objectives were not repeated in this final analysis, except subgroup analyses of the primary objective ORR at Day 28 were re-analysed based on additional data collected up to final database lock and post-hoc sensitivity analyses were conducted as described in statistical methods section below.

Other secondary objectives

The following secondary objectives were analysed in the final analysis.

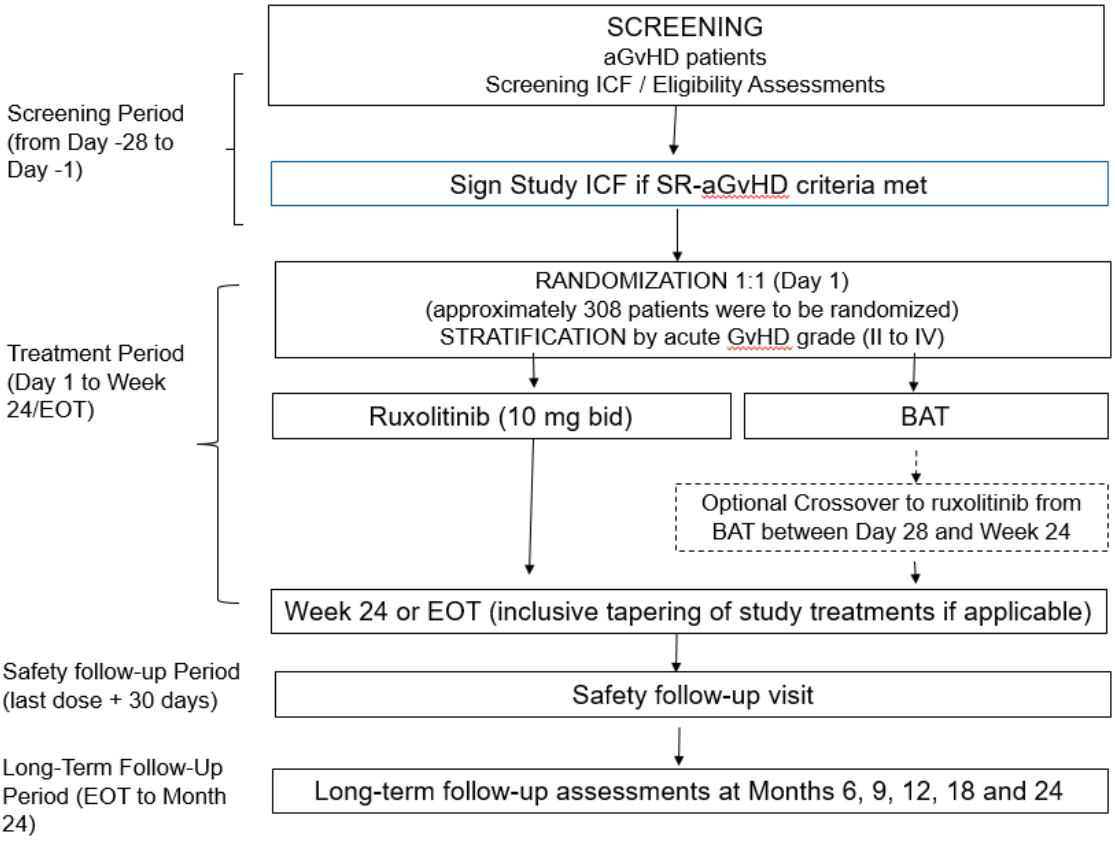
- Duration of response
- Cumulative steroid dose until Day 56, and until EOT (only for final analysis)
- Overall Survival (OS)
- Event-Free Survival (EFS)
- Failure-Free Survival (FFS)
- Non-Relapse Mortality (NRM)
- Malignancy Relapse/Progression (MR)
- Incidence of cGvHD
- Changes in Patient Reported Outcomes (PROs)
- To assess Pharmacokinetics (PK) of ruxolitinib in SR-aGvHD patients
- Safety of ruxolitinib and Best Available Therapy

Study design

This randomized, Phase III, open-label study investigated the efficacy and safety of ruxolitinib vs. BAT added to the patient's immunosuppressive regimen in adults and adolescents (≥12 years old) with grade II-IV SR-aGvHD.

The study schematic is presented in Figure 1-1.

Figure 1-1 Schematic study design



Patients randomized to the BAT arm were allowed to crossover to the ruxolitinib arm if they did not demonstrate complete or partial response at Day 28 between Day 28 and Week 24 or if they lost their response and met criteria for progression, mixed response, or no response, necessitating new additional systemic immunosuppressive treatment for aGvHD.

Study population /Sample size

With a total of 308 patients planned to be enrolled with a 1:1 randomization (ruxolitinib vs. BAT) and stratified on aGvHD grade (Grade II vs. Grade III vs. Grade IV) the study would have 90% power to test for the primary endpoint (ORR at Day 28) and approximately 90% power to test for the key secondary endpoint (durable ORR at Day 56).

A total of 310 patients with SR-aGvHD were enrolled, out of which 309 patients were included in the analysis (as one patient did not sign the study informed consent prior to receiving BAT (protocol deviation) and was excluded from all analyses), comprising 9 adolescent (2.9%) patients between 12 to <18 years of age.

Diagnosis and main criteria for inclusion: Patients eligible for inclusion in the study had to meet all of the following criteria:

- Written screening informed consent and/or assent from the patient, parent, or guardian at the time of Screening, i.e. at the time of aGvHD Grade II-IV diagnosis.
- Written study informed consent and/or assent from the patient, parent, or guardian once SR-aGvHD was confirmed.
- Male or female patients aged 12 or older at the time of screening informed consent.
- Able to swallow tablets.
- Had undergone Allogeneic Stem Cell Transplantation (alloSCT) from any donor source (matched unrelated donor, sibling, haplo-identical) using bone marrow, peripheral blood stem cells, or cord blood. Recipients of non-myeloablative, myeloablative, and reduced intensity conditioning were eligible.
- Clinically diagnosed Grades II to IV acute GvHD as per standard criteria occurring after alloSCT requiring systemic immune suppressive therapy. Biopsy of involved organs with aGvHD was encouraged but not required for study screening.
- Evident myeloid and platelet engraftment (confirmed within 48h prior to study treatment start):
    - Absolute neutrophil count (ANC) > 1000/mm^3

    and

    - Platelets $\geq$ 20,000/ mm^3

    Note: Use of growth factor supplementation and transfusion support was allowed.
- Confirmed diagnosis of SR-aGvHD

Key exclusion criteria: Patients eligible for this study should not have met any of the following key criteria:

- Received more than one systemic treatment for SR-aGvHD.
- Clinical presentation resembling de novo chronic GvHD or GvHD overlap syndrome with both acute and chronic GvHD features.
- Failed prior alloSCT within the past 6 months.
- Presented with relapsed primary malignancy, or patients who were treated for relapse after the alloSCT was performed, or who may require rapid immune suppression withdrawal as pre-emergent treatment of early malignancy relapse.
- SR-aGvHD occurring after non-scheduled Donor Lymphocyte Infusion (DLI) administered for pre-emptive treatment of malignancy recurrence.
- Presented with active uncontrolled infection including significant bacterial, fungal, viral or parasitic infection requiring treatment.
- Presented with evidence of uncontrolled viral infection including Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Human Herpes Virus (HHV-6), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) based on assessment by the treating physician.

Treatments

The study treatment consisted of ruxolitinib or Investigator-choice BAT administered in an open label manner following randomization of the patient on study Day 1 in combination with corticosteroids ± calcineurin inhibitors (CNI).

Ruxolitinib was administered orally twice per day at a dose of 10 mg bid, as two 5-mg tablets. Ruxolitinib was taken without regard to food.

Best available therapy: Patients received BAT based on the investigator's best judgment. The BAT in this study was identified by the investigator prior to patient randomization among the following treatments currently used in this setting: anti-thymocyte globulin (ATG), extracorporeal photopheresis (ECP), mesenchymal stromal cells (MSC), low-dose methotrexate (MTX), mycophenolate mofetil (MMF), mTOR inhibitors (everolimus or sirolimus), etanercept, or infliximab. No other types or combinations of BAT were permitted. BAT was sourced from the local market in each participating country.

Other study treatments: Calcineurin inhibitor (CNI) and systemic corticosteroids could be taken by the patient as per standards of care.

Other permitted concomitant therapies: Patients who undergo alloSCT are at risk for a variety of infections based on the degree of immunosuppression induced by the conditioning regimen prior to transplant. Therefore, antibiotics, anti-infectives, and immunizations could be used as prophylactic therapies for infections.

Outcomes/endpoints

Efficacy:

- **aGvHD assessment**: Acute GvHD grading was performed by the investigator at every visit during the treatment period and at EOT visit. aGvHD was graded using standard staging criteria for aGvHD (Harris et al 2016): measures of body surface area aGvHD skin rash, stool volumes or frequency per 24 h time period, and serum bilirubin levels, staging by organ (skin; liver; upper gastro-intestinal; lower gastro-intestinal) and overall grading at the time of the evaluation. In addition, biopsy of the organ involved could be performed per institutional practices at Investigator's discretion for aGvHD management. Once randomized, response to study treatment was assessed by the Investigator at every visit during the Treatment Period according to study protocol definition.
- **Chronic GvHD assessment**: Occurrence of definitive and possible manifestations of cGvHD was assessed monthly from Day 1 to Day 56 and at every visit thereafter during the treatment period, at the time of last dose if before Week 24, in responding patients, and at EOT (or Crossover EOT). After EOT (or Crossover EOT), patients were assessed for occurrence of cGvHD at the Safety Follow-up visit if applicable, and at Month 6, at Month 9, at Month 12, at Month 18 and at Month 24 during the Long-Term Follow-up period. Occurrence of cGvHD was not considered an adverse event (AE). cGvHD was graded as per NIH consensus guidelines for cGVHD, as mild, moderate, or severe at the time of cGvHD diagnosis.
- **Graft failure monitoring**: Patients were monitored for any evidence of secondary graft failure at each visit from Day 1 during the Treatment, at the time of last dose if before Week 24, in responding patients, at EOT (or Crossover EOT), Safety Follow-up if applicable, and Long-Term Follow-up periods. Occurrence of graft failure was reported as an event and also as an AE. Graft failure was defined as initial whole blood or marrow donor chimerism ≥5% declining to

<5% on subsequent measurements. Donor chimerism was closely monitored to detect graft failure.

- **Chimerism**: Donor chimerism after a hematopoietic stem cell transplant involves identifying the genetic profiles of the recipient and of the donor pre-transplant, and then evaluating the ratio of donor to recipient cells in the recipient's blood, or bone marrow. Chimerism testing using peripheral blood mononuclear cells or bone marrow (or peripheral blood selected CD3+ T cells) was performed during screening (prior to study treatment start), at Day 28 and at Day 56. In addition, for patients who Crossover from BAT to ruxolitinib, chimerism was also performed at Crossover Week 1. Additional chimerism testing could be performed at any time during study (Treatment and Long-Term Follow-up period) at the treating Investigator's discretion according to local institutional practice as indicated.
- **Hematologic disease relapse/progression assessment**: Patients were monitored for any evidence of underlying hematologic disease relapse or progression during the study. Patients were assessed at each visit from Day 1 during the Treatment period, including during crossover period if applicable, at the time of last dose if before Week 24, in responding patients, at EOT (or Crossover EOT), Safety Follow-Up if applicable, and the Long-Term follow-up period.

  The relapse and progression of the underlying hematologic disease were assessed by the Investigator as per the definitions outlined in protocol.

  Evaluation and/or evidence of malignancy relapse/progression was conducted according to local institutional practices. Per protocol, study treatment was discontinued underlying hematological disease progression or relapse.

Patient-reported outcomes: In order to measure Quality-of-Life (QoL) among aGVHD patients, and potential changes over time, two patient-reported outcome (PRO) instruments were administered: FACT-BMT (only adult patients) and EQ-5D-5L.

Pharmacokinetics: Blood sampling for PK of ruxolitinib was performed in all patients enrolled in the study and treated with ruxolitinib to characterize the PK parameters in aGvHD patients.

Extensive PK sampling schedule: "Extensive PK" sampling schedule was followed for approximately the first twenty-five (25) adult patients and all adolescent patients enrolled. The 'Extensive PK' sampling scheme includes a pre-dose and seven (7) post-dose samples on Day 1 and Day 7 thereafter, two (2) samples (1 pre-dose and 1 post-dose) per scheduled visit.

Sparse PK sampling schedule: Adult patients randomized to ruxolitinib after the Extensive PK samples were collected, and any patients crossing over from BAT to ruxolitinib after Day 28, would follow the "Sparse PK" sampling schedule and had a total of two (2) samples (1 pre-dose and 1 post-dose) per scheduled visit. The plasma samples from all patients were assayed for ruxolitinib concentrations using validated liquid chromatography-tandem mass spectrometry method.

Safety: Safety was monitored by assessing physical examination, vital signs, height and weight, and laboratory assessments including urinalysis, assessment of pregnancy and fertility, clinical chemistry and hematology. Adverse event data was collected at every visit until the 30-day safety evaluation follow-up. Afterwards, only SAEs suspected with a causal relationship to study treatment as assessed by the Investigator were collected.

Special safety assessments included:

- Bleeding, due to the potential complications of thrombocytopenia and/or coagulopathy in the setting of alloSCT.

- Infection monitoring identified as a risk associated with ruxolitinib and BAT for aGvHD therapy.
- Viral reactivation monitoring for hepatitis B and C (HBV viral DNA-PCR and HCV RNA-PCR), Cytomegalovirus (CMV viral DNA quantification), Epstein Barr Virus (EBV viral load), Human Herpes virus (HHV-6 viral load).
- Second primary malignancy monitoring defined as any new malignancy other than the underlying hematologic disease.
- Pulmonary function test (PFT), if indicated clinically at investigator's discretion per local practices.

Statistical Methods

The primary endpoint ORR at Day 28 was evaluated in the primary analysis and secondary analyses (re-analyzed subgroup analyses); and was not repeated in this final analysis, except subgroup analyses were repeated and post-hoc sensitivity analyses were conducted.

- A post-hoc sensitivity analysis with exclusion of the subjects who had protocol deviations of organ staging and/or aGvHD response assessments performed per investigator judgement, not strictly following standard criteria defined in study protocol at Day 28
- A post-hoc sensitivity analysis with exclusion of the subjects with aGvHD grade <II at baseline

The key secondary endpoint durable ORR at Day 56 was evaluated in the primary analysis and secondary analyses; and was not repeated in this final analysis, except a post-hoc sensitivity analysis was conducted with exclusion of the subjects who had protocol deviations of organ staging and/or aGvHD response assessments performed per investigator judgement, not strictly following standard criteria defined in study protocol at Day 56

ORR at Crossover Day 28 was defined as the proportion of crossover patients with CR or PR at Crossover Day 28 according to standard criteria. ORR was summarized using descriptive statistics (N, %) along with two-sided exact binomial 95% CIs based on the Crossover analysis set (CAS) using local Investigators' review of aGvHD assessment data.

Durable ORR at Crossover Day 56 was defined as the proportion of all crossover patients who achieved a CR or PR at Crossover Day 28 and maintained a CR or PR at Crossover Day 56. Durable ORR at Crossover Day 56 was summarized using descriptive statistics (N, %) along with two-sided exact binomial 95% CIs based on the CAS using local investigators' review of aGvHD assessment data.

Analysis of secondary efficacy objectives

The other secondary efficacy objectives were to evaluate the two treatment arms with respect to:

- Duration of response: DOR was defined for patients who had a CR or PR at Day 28. This was the interval between the date of first documented response of CR or PR (i.e., the start date of response), till the date of progression or addition of systemic therapies for aGvHD on or after Day 28.
- Overall survival: OS was defined as the time from date of randomization to date of death due to any cause. If a patient was not known to have died, then OS was censored at the latest date the patient was known to be alive (on or before the cut-off date).
- Event free survival: EFS was defined as the time from the date of randomization to the date of hematologic disease relapse/progression, graft failure or death due to any cause.

- Failure free survival: FFS was defined as the time from the date of randomization to date of hematologic disease relapse/progression, non-relapse mortality or addition of new systemic aGvHD treatment.
- Non-relapse mortality: NRM was defined as the time from date of randomization to date of death not preceded by hematologic disease relapse/progression.
- Incidence of malignancy relapse/progression: MR was defined as the time from date of randomization to hematologic malignancy relapse/progression.
- Incidence of cGvHD: Incidence of cGvHD was the time from date of randomization to onset of cGvHD. Deaths without prior onset of cGvHD and hematologic disease relapse/progression were competing risks.
- Cumulative steroid dosing until Day 56: Overall and weekly cumulative steroid dose for each patient up to Day 56 or discontinuation of randomized treatment was tabulated. In addition, the relative dose intensity (RDI), by week, was calculated relative to the starting dose of corticosteroids and categorized as (1) complete reduction where patients are tapered off corticosteroids by Day 56, (2) ≤50% RDI and (3) >50% RDI. Additionally, in the final analysis, the proportion of patients with any dose or 50% reduction of corticosteroids dose until Day 56 from baseline have been also provided. Among those patients who reduced the dose of corticosteroids, the percentage change in dose from baseline to Day 56, and the maximum of dose reduction during the period were calculated using descriptive statistics.
- Cumulative steroid dosing until EOT: In the final analysis, the proportion of the complete reduction of corticosteroids by EOT (i.e., patients tapered off corticosteroids by EOT) have been provided. In addition, the proportion of patients with any dose or 50% reduction of corticosteroids dose until EOT from baseline have been provided. Among those patients who reduced the dose of corticosteroids, the percentage change in dose from baseline to EOT, and the maximum of dose reduction during the period were calculated using descriptive statistics.

All the secondary efficacy endpoint analyses were non-comparative in nature and were analyzed using the FAS.

Safety: All safety analyses were based on Safety Set, except that the summary of safety data during the crossover treatment phase were based on CAS. All listings and tables were presented by treatment group.

Due to possible crossover from BAT to ruxolitinib arm after Day 28, imbalance in exposure between the two arms was expected. Therefore, safety summaries for the randomized treatment were produced for the following periods, unless specified:

- Up to Day 31 (the upper bound of the Day 28 visit window);
- Up to the earlier of i) cutoff date, ii) end date of on-randomized-treatment period.

Safety summaries (tables, figures) included only data from the on-treatment period with the exception of baseline data which were also summarized where appropriate (e.g. change from baseline summaries).

The data from on-randomized-treatment period and on-crossover-treatment period were summarized separately. In addition, a separate summary for death including on-treatment and post-treatment deaths was provided.

In order to account for differences in exposure of the ruxolitinib arm relative to the BAT arm due to crossover from BAT to ruxolitinib after Day 28 visit, incidence rates of adverse events were also presented by adjusting for duration of treatment period in patient-years where relevant.

Laboratory data collected up to the end of the on-treatment period (randomized or crossover period) were summarized. Laboratory values were graded as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Vital sign assessments were performed in order to characterize basic body function.

In addition to the analysis of infections by standard CTCAE grading, the infection grading system developed by Cordonnier and validated for alloSCT patients predictive of mortality was also used in this study. Cumulative incidence curve for time to grade 3 severity infection as well as estimates at 1, 2 and 6 months with 95% CIs were presented for each treatment group. In addition, the median time to occurrence of infection was calculated. Simple descriptive statistics, median, min and max as well as 25th percentile and 75th percentile, were presented.

Results

Recruitment/ Number analysed/ Baseline data

Demographic and background characteristics

Baseline demographics were well-balanced between the two treatment arms. The median age in the overall population was 54 years (range: 12.0 to 73.0). The proportion of male and female patients was 59.2% and 40.8%. Most patients were White (68.9%).

The study population included 9 adolescent (2.9%) patients between 12 to <18 years of age, with a median age (range) of 15 years (range: 12.0 to 16.0) and majority of them being White (77.8%).

Baseline disease characteristics

Underlying disease history: Baseline disease characteristics were similar between the two treatment arms. Majority of enrolled patients had malignant underlying disease including leukaemia/ myelodysplastic syndrome (83.8% in ruxolitinib arm, and 78.1% in BAT arm).

Transplant-related history: Most patients (75.4%) entered the study with low hematopoietic cell transplantation (HCT)-comorbidity scores (between 0 and 2). There were minor differences in the type of conditioning regimen received prior to transplant between the treatment arms. In the ruxolitinib arm, 55.2% of patients received myeloablative conditioning prior to transplant compared to 41.9% in BAT arm. Consequently, fewer patients in ruxolitinib arm received the less intense forms of conditioning therapy (non-myeloablative: 20.1% and reduced intensity: 24.7%) compared to BAT arm (non-myeloablative: 26.5% and reduced intensity: 31.6%). T-cell depletion was performed in 39 (12.6%) patients overall, including 17 patients (11.0%) in ruxolitinib arm and 22 (14.2%) patients in BAT arm. Peripheral blood was the most common source for SCT (87.0% in ruxolitinib arm and 76.8% in BAT arm), and most patients received grafts from identical human leukocyte antigen (HLA)-matched donors (59.0%; 183/310). The donor was related to the transplant recipient in 33.5% patients, in slightly fewer patients in ruxolitinib arm (31.6%) than in BAT arm (35.5%).

Median total nucleated dose was similar between the two arms (ruxolitinib: 35.1 x 10E7 NC/kg, range: 0.2 to 13020.0; BAT: 35.0 x 10E7 NC/kg, range: 0.2 - 7416.0).

aGvHD disease history: Acute GvHD disease history was similar between the two treatment arms. The number of patients at baseline with grade II, III, and IV aGvHD in ruxolitinib and BAT arms were: 47 (30.5%) vs. 54 (34.8%), 70 (45.5%) vs. 67 (43.2%) and 31 (20.1%) vs. 33 (21.3%), respectively.

Median time to conversion from grade II to IV aGvHD to SR-aGvHD was 10 days (range: 1.0 to 331.0). The most frequently used prior aGvHD therapy was steroid + CNI + Other systemic aGvHD treatment (47.4% in ruxolitinib arm and 43.9% in BAT arm), with most patients in the sub-category Steroid + CNI + only aGvHD prophylaxis (36.4% in ruxolitinib arm and 31.0% in BAT arm).

Median time from diagnosis of SR-aGvHD to randomization was 1 day (range: 0.0 to 47.0). The most common reason for SR-aGvHD was failure to achieve a response after 7 days of treatment with steroids (46.8% in ruxolitinib arm and 41.3% in BAT arm). Among all patients, the most common organs involved at randomization were skin (overall 54.0%; 60.4% in ruxolitinib arm and 47.7% in BAT arm) and lower GI tract (overall 68.3%; 62.3% in ruxolitinib arm and 74.2% in BAT arm). More patients in the ruxolitinib arm had symptoms of skin (60.4%) and liver (24.0%), than BAT arm (skin: 47.7% and liver: 16.1%). Upper GI and lower GI aGvHD involvement were less frequent in ruxolitinib arm (18.2% and 62.3%) than in BAT arm (23.9% and 74.2%).

Efficacy results

Overall, at the time of final analysis, the efficacy endpoint results remained in line with previous observations (Secondary and Primary analyses). Ruxolitinib showed sustained efficacy with longer follow-up.

- The study met the primary endpoint and results were presented in the Primary analysis CSR and same results are presented again in this report. The ORR on Day 28 was 62.3% (95% CI: 54.2, 70.0) in the ruxolitinib arm and 39.4% (95% CI: 31.6, 47.5) in the BAT arm. There was a statistically significant difference between the treatment arms (stratified Cochrane-Mantel-Haenszel test p<0.0001, one-sided, odds ratio: 2.64 with 95% CI: 1.65, 4.22).
- Subgroup analysis based on additional data collected up to final database lock indicated consistent results with that of primary analysis for overall population. The OR was in favour of ruxolitinib across most of baseline characteristics subgroups, including aGvHD grade at randomization, organ involvement, donor match status, criteria for SR, prior aGvHD therapy and graft source, as well patients from various regions (Australia, Europe and Canada, and from Japan).
- Post-hoc sensitivity analyses performed excluding subjects with protocol deviations of organ staging and/or aGvHD response assessments per investigator judgement at Day 28 (ORR of 63.0% in ruxolitinib arm and 37.5% in BAT arm; odds ratio in favor of ruxolitinib: 2.87; 95% CI: 1.77, 4.65; p<0.0001) and excluding subjects with aGvHD grade <II at baseline (ORR of 63.5% in ruxolitinib arm and 39.6% in BAT arm; odds ratio in favor of ruxolitinib: 2.75; 95% CI: 1.71, 4.41; p<0.0001) showed results similar to the primary analysis
- Durable ORR at Day 56 (key secondary endpoint) analyzed at the Primary analysis cut-off, showed statistically significant difference between two arms and in favor of ruxolitinib (39.6% in ruxolitinib arm and 21.9% in BAT arm; odds ratio: 2.38; 95% CI: 1.43, 3.94; p=0.0005). A post-hoc sensitivity analysis performed excluding subjects with protocol deviations of organ staging and/or aGvHD response assessments per investigator judgement at Day 56 showed results similar to the primary analysis, with durable ORR of 39.3% in ruxolitinib arm and 20.9% in BAT arm; an odds ratio of 2.50 (95% CI: 1.48, 4.22; p=0.0004).
- Median duration of response was longer in ruxolitinib arm (167 days, range: 22.0 to 677) than in BAT arm (106 days, range: 10 to 526).
- There was a 15% reduction in risk of death in ruxolitinib arm relative to BAT arm (HR: 0.85; 95% CI: 0.63, 1.14), which was not statistically significant (log-rank p-value: 0.2800). OS

median follow-up time was longer in ruxolitinib arm (8.23 months) compared to BAT arm (3.81 months). K-M estimated median OS was also longer in ruxolitinib arm (10.71 months) compared to BAT arm (5.82 months).

- There was a 15% reduction in risk of EFS event in ruxolitinib arm relative to BAT arm (HR: 0.85; 95% CI: 0.64, 1.13), which was not statistically significant (log-rank p-value: 0.2723). K-M estimated median EFS was longer in ruxolitinib arm (8.28 months) compared to BAT arm (4.17 months).
- There were fewer FFS events in ruxolitinib arm (59.1%) than in BAT arm (78.1%). Median FFS with ruxolitinib was statistically significantly longer than with BAT (4.86 months vs. 1.02 months; HR: 0.51, 95% CI: 0.39, 0.66; p<0.0001).
- The cumulative incidence curves for NRM were overlapping for ruxolitinib and BAT arms, indicating similar event rates between the arms over time.
- Sensitivity analyses based on longer follow-up for EFS and FFS including aGvHD progression as an event and for NRM including patients with underlying hematologic malignant disease, showed similar results as primary analysis.
- There were few events of malignancy relapse/progression in both treatment arms (13.6% in ruxolitinib arm and 17.0% in BAT arm), suggesting that graft versus leukemia effect was maintained while treating GvHD patients.
- At Day 56, more patients in ruxolitinib arm (22.1%) had tapered off corticosteroids than in BAT arm (14.8%). Most patients in both treatment arms had any dose reduction (91.6% and 87.1%) or at least 50% dose reduction (76% and 71.6%) of corticosteroids by Day 56. The dose reduction achieved at Day 56 was greater in patients in ruxolitinib arm than the BAT arm (-59.9% vs -52.4%; maximum reduction: -71.7% vs -64.6%). Similar trend was seen for complete tapering and reductions of steroid dosing until EOT.
- Up to the end of study, a total of 33.8% patients in ruxolitinib arm and 21.9% patients in BAT arm had developed cGvHD. Number of patients with competing risks were similar between the treatment arms. The median onset time of cGvHD was longer in ruxolitinib arm (217.5 days) than the BAT arm (185 days). Also, majority of cGvHD events were mild at time of onset in both treatment arms and there were fewer cases of severe cGvHD in ruxolitinib arm (6 patients) than in BAT arm (8 patients).
- In both the randomized treatment and crossover periods, there was an overall improvement in all aspects of EQ-5D-5L and FACT-BMT questionnaires in both arms, more pronounced in the ruxolitinib arm than in BAT arm.
- A small proportion of patients (10/309) experienced graft failure until the end of study, this included 5 patients each in ruxolitinib arm and BAT arm.
- There were no remarkable differences in hospitalizations between the two treatment arms up to the end of treatment period.

Pharmacokinetic results:

- PK parameters for exposure after continuous dosing for 7 days were comparable to Day 1, and there was no indication of accumulation. After 7 days of continuous dosing, geometric mean $C_{ma}x$ was 129.3 ng/mL and AUC_{tau} was 651.9 ng.h/mL in patients with aGvHD.

- PK parameters at Day 1 in adolescent patients could be computed for only 4 patients, however, within the ambit of the available data, the exposure in adolescent patients was within the range observed in adult patients.

Safety results

The overall safety profile at the end of study was consistent with that observed in the previous analyses (Primary analysis and Secondary analysis).

The median duration of exposure to ruxolitinib was longer (63 days; range: 6 to 678) than to BAT (29 days; range: 1 to 188). Overall exposure was longer in the ruxolitinib arm (40.6 vs. 18.9 PTY). The data presented in this section needs to be interpreted with caution given the significant difference in the duration of exposure between the two treatment groups and taking into account the sensitivity analyses adjusted for exposure.

- A similar proportion of patients in both treatment arms (ruxolitinib and BAT) experienced at least one AE up to Day 28 (96.7% and 94.7%) as well as during randomized treatment period (99.3% and 98.7%). In the Crossover period, the overall incidence of AEs (98%) was consistent with that of the ruxolitinib arm during randomized treatment period.
- Infections and infestations, blood and lymphatic system disorders, investigations, gastrointestinal disorders and metabolism and nutrition disorders were SOCs with most common AEs up to both Day 28 and during randomized treatment period.
- During randomized treatment period, the difference in incidence of all AEs by SOC between treatment arms (ruxolitinib vs. BAT) was ≥10% only for infections and infestations (81.6 vs. 71.3%), blood and lymphatic system disorders (72.4% vs. 50.7%), gastrointestinal disorders (63.8% vs. 50.0%) and investigations (58.6% vs. 46.0%), which were more frequent in ruxolitinib arm than in the BAT arm.
- The most common AEs in both treatment arms were cytopenia and CMV infection reactivation
- Up to Day 28, the most frequent AEs were thrombocytopenia (32.9% vs. 18%), anaemia (30.3% vs. 27.3%), and CMV infection reactivation (22.4% vs. 16.7%).
- During randomized treatment period, the most frequent AEs were anaemia (40.1% vs. 31.3%), thrombocytopenia (36.8% vs. 20%) and CMV infection reactivation (25% vs. 20.7%).
- Consistent with the observations up to Day 28, the incidence of AEs suspected to be related to study treatment during randomized treatment period was higher in the ruxolitinib arm compared to BAT arm, driven by higher frequency of AEs from SOCs of blood and lymphatic system disorders, investigations, infections and infestations and GI disorders in the ruxolitinib arm. Thrombocytopenia (23.0%), anaemia (17.1%), platelet count decreased (14.5%), neutropenia (13.8%), WBC count decreased (9.9%), neutrophil count decreased (8.6%), leukopenia (6.6%) and CMV infection reactivation (4.6%) were the most common PTs suspected to be related to study treatment in ruxolitinib.
- During randomized treatment period, the overall incidence of Grade ≥3 AEs was similar between the two treatment arms (91.4% in ruxolitinib arm and 87.3% in BAT arm). The incidence of these AEs by PT was also similar, except for anaemia (35.5% vs 24.7%) and thrombocytopenia (33.6% vs 16%) that occurred more frequently in the ruxolitinib arm than in BAT arm.
- When adjusted for exposure, the overall incidence of all grade AEs during randomized treatment period was higher in the ruxolitinib arm than in the BAT arm (5262.7 events/100

PTY vs. 4733.5 events/100 PTY). However, the overall incidence of Grade ≥3 AEs was higher in the BAT arm than in the ruxolitinib arm (1440.8 events/100 PTY vs. 1329.1 events/100 PTY). Exposure adjusted incidence rate of PT thrombocytopenia was higher in the ruxolitinib arm than in the BAT arm (152.6 vs. 118.7).

- There was no definite trend in the probability of events from 0 to 6 months in either treatment arm. The probability of AEs was lower towards the end of the assessment period (i.e., beyond 6 months). The probability of AEs was similar between both treatment arms over time.
- A total of 43 (28.3%) and 36 (24.0%) on-treatment deaths occurred in the ruxolitinib and BAT group, respectively. The most common cause of death was the study indication (including aGvHD and/or complications attributed to treatment for aGvHD) and related conditions in both ruxolitinib (21; 13.8%) and BAT arms (21; 14.0%). Other common causes of death were sepsis (3; 2.0%), cardiac arrest, disease progression, multiple organ dysfunction syndrome and septic shock (2; 1.3% each) in ruxolitinib arm; and sepsis and septic shock (2; 1.3% each) in BAT arm. A total of 14 on-treatment deaths were suspected to be related to the study treatment, more in ruxolitinib arm (10 patients) than in BAT arm (4 patients). No new on-treatment deaths occurred after the Primary analysis cut-off date.
- Up to Day 28, a similar proportion of patients in both ruxolitinib arm (37.5%) and BAT arm (34.0%) experienced an SAE. During randomized treatment period, SAEs were observed in 66.4% patients in the ruxolitinib group and 53.3% patients in the BAT group. The SAE pattern remained consistent with the observations at Primary analysis and Secondary analysis cut-offs.
- When adjusted for exposure, the overall incidence of SAEs was higher in the BAT arm (424.3 events/100 PTY) than in the ruxolitinib arm (307.0 events/100 PTY).
- SAEs with a fatal outcome occurred in similar proportion of patients in the ruxolitinib arm and BAT arm (21.7% vs. 21.3%). Sepsis (5.3% vs 2.7%) and septic shock (4.6% vs 2.7%) were the most common SAEs with a fatal outcome in both treatment arms. No new SAEs with fatal outcome were reported after the primary analysis cut-off date.
- By PT, the most frequent (≥5% patients in either treatment arm) SAEs were sepsis, septic shock, pyrexia, pneumonia, diarrhoea and CMV infection reactivation.
- The incidence of SAEs suspected to be related to study treatment was higher in the ruxolitinib arm compared to BAT arm (27.6% vs. 12.7%), which was mainly driven by higher incidence of suspected SAEs in the SOCs infections and infestations (14.5% vs 7.3%) and blood and lymphatic system disorders (5.3% vs 0.7%).
- During randomized treatment period, AEs leading to study treatment discontinuation were observed in more patients in the ruxolitinib arm (27.6%) than in the BAT arm (9.3%). The most common (≥2% or >2 patients) AEs leading to discontinuation in the ruxolitinib arm were neutropenia, sepsis, anaemia, pancytopenia and thrombocytopenia. In the BAT arm, except thrombocytopenia (3 patients), respiratory failure and septic shock (2 patients each), all AEs leading to discontinuation were observed in one patient each
- During randomized treatment period, AEs leading to dose adjustment or interruption were higher in ruxolitinib arm (54.6%) than in BAT arm (12.7%), driven by cytopenia, including thrombocytopenia (13.8% vs. 0.7%), neutropenia (11.8% vs. 0.7%), platelet count decreased (11.2% vs. 2.7%) and leukopenia (5.3% vs. 0.7%).
- During randomized treatment period, AEs requiring additional therapy were observed in similar proportion of patients in ruxolitinib and BAT arms (97.4% and 94%). Most common (≥20%)

AEs requiring additional therapy in both treatment arms were anemia (32.2% vs. 26.7%) and CMV infection reactivation (24.3% vs. 20.7%).

- During randomized treatment period, the overall incidence of cytopenia was higher in ruxolitinib arm compared to BAT arm. Thrombocytopenia events were more frequently reported (56.6% in ruxolitinib and 36.0% in BAT arm). When adjusted for exposure, the incidence of thrombocytopenia events was 304.5 and 246.4 per 100 PTYs in ruxolitinib and BAT arms. Cytopenia is expected consequence due to mechanism of action of ruxolitinib.
- The infection events were frequently reported in both treatment arms as expected in this study population; 82.2% in ruxolitinib arm and 71.3% in BAT arm during randomized treatment period. Corresponding exposure-adjusted IRs of infections excluding tuberculosis events were 687.7 and 791.3 per 100 PTYs in ruxolitinib and BAT arms respectively. The most frequently occurring PTs in ruxolitinib and BAT arms were cytomegalovirus infection reactivation (25.0% vs. 20.7%), sepsis (11.2% vs. 12.7%), pneumonia (11.2% vs. 9.3%) and urinary tract infection (10.5% vs. 6.7%).
- During randomized treatment period, the proportion of patients with bleeding (hemorrhage) events was higher in ruxolitinib arm compared to the BAT arm (40.1% vs. 28.0%). When adjusted for exposure, the incidence of hemorrhage events was 153.0 and 174.3 per 100 PTYs in ruxolitinib and BAT arms. Hematuria was most frequently reported PT in both arm (7.9% in ruxolitinib arm and 4.7% in BAT arm). When adjusted for exposure, the incidence of PT hematuria was similar between the two treatment arms (24.6 vs. 24.4 events/100 PTY).
- Subgroup analyses of AEs during randomized treatment period:
    - The observations from subgroup analysis by age, race and gender remained consistent with previous analyses (Primary analysis and Secondary analysis) and no major changes were observed. Overall, the profile of AEs was similar between the age groups and races. However, due to the disparity in number of patients across the age groups and races, it is difficult to conclude on any trends for AEs.
    - The observations from subgroup analysis by region and by aGvHD organ involvement at baseline remained consistent with the Secondary analysis (not analyzed at Primary analysis cut-off). Overall, the AE profile remained similar between these subgroups.
- During randomized treatment period, abnormal hematological parameters were observed in patients from both treatment arms.
- Majority of the patients had low platelet count and low haemoglobin at baseline. The proportion of patients with post-baseline grade 4 low platelet count was higher in ruxolitinib than BAT arm (53.9% vs. 46.0%). Grade 3 worsening of low haemoglobin level from baseline was comparable between treatment arms (47.4% vs 46.0%). There were no patients with Grade 4 low haemoglobin.
- WBC counts were within normal limits in majority of patients at baseline. Grade 3 (ruxolitinib: 32.9% vs. BAT: 24.0%) or Grade 4 (ruxolitinib: 24.3% vs. BAT: 24.0%) worsening (decrease) of WBC counts from baseline were comparable between treatment arms. Grade 3 or 4 values for low neutrophil and low lymphocyte counts were comparable between treatment arms.
- During randomized treatment period, elevation of ALT, AST, bilirubin, alkaline phosphatase and GGT was noted in many patients. Of note, the liver is one target organ of underlying study indication.

In the majority of patients, the worsening post-baseline was to grade 1 or 2. Grade 3 abnormalities were comparable between the treatment arms and grade 4 abnormalities were less frequent in both treatment arms. A total of 7 (4.6%) patients in ruxolitinib arm and 12 (8%) patients in BAT arm met the criteria for Hy's law.

- Notable vital sign values during randomized treatment period were comparable between ruxolitinib and BAT arms.

Safety in adolescents

9 adolescent patients (5 in ruxolitinib arm and 4 in BAT arm) were analysed for safety in the Study C2301. The median duration of exposure to ruxolitinib was longer (163 days; range: 11 to 242) than to BAT (58 days; range: 2 to 162). The exposure duration in the ruxolitinib arm was 1.7 patient years.

Overall, the safety profile of ruxolitinib in adolescents was considered similar to that of respective overall populations. Some of the frequent AEs observed in the adolescent patients were related to Primary system organ class (SOC) of Blood and lymphatic system disorders (4 patients in the ruxolitinib arm and 2 patients in the BAT arm) and Infections and infestations (3 patients in the ruxolitinib arm and 3 patients in the BAT arm) and Gastrointestinal disorders (3 patients in the ruxolitinib arm and 2 patients in the BAT arm). Cardiac disorders, vascular disorders, and immune system disorders were not observed in patients between 12 to 18 years of age treated with ruxolitinib. The profile of suspected AEs and SAEs were similar to the adult patients. Given the limited number of patients in the adolescents group, results should be interpreted with caution.

Up to the end of the study follow up period, 4 deaths were reported in adolescent patients. One death was observed in the BAT arm due to study indication and 3 deaths in patients randomized to the ruxolitinib arm (reason reported in one patient each: underlying malignancy progression, respiratory failure and infection).

Fertility, pregnancy, birth and lactation

There are no new human data on the effect of ruxolitinib on fertility. There were no reported pregnancies or lactation events reported during treatment with ruxolitinib for aGvHD.

Safety conclusions

The overall safety profile at the end of study was consistent with that observed in the previous analyses (Primary analysis and Secondary analysis). The safety of ruxolitinib in aGvHD is well characterized and is consistent with its established safety profile. The safety profile of ruxolitinib in adolescents is considered similar to that of respective overall population.

In conclusion, ruxolitinib administered according to the recommended dose regimen of 10 mg b.i.d remains favorable for the treatment of GvHD patients 12 years of age and older who had inadequate response to corticosteroids or other systemic therapies. The overall safety profile is consistent with the previously known safety profile of ruxolitinib and as expected in the GvHD population and appears to be effectively manageable. No new or unexpected safety concerns were identified, of note no significant imbalance between ruxolitinib and BAT was observed in regard to the incidence of infections.

2.3.3. Discussion on clinical aspects

A final report for the study CINC424C2301 in accordance with Article 46 of Regulation (EC) No1901/2006 was submitted. This Phase III randomized study was conducted to investigate the

efficacy and safety of ruxolitinib versus investigator-choice BAT added to the patient's immunosuppression regimen in adults and adolescents ≥ 12 years old with Grade II-IV SR-aGvHD.

A total of 309 patients were included in the Full Analysis Set, 154 were in the ruxolitinib arm and 155 were in the BAT arm. The study population included 9 adolescent (2.9%) patients between 12 to <18 years of age, 5 in the Ruxolitinib arm and 4 in the BAT arm.

The study met the primary endpoint. The ORR on Day 28 was 62.3% (95% CI: 54.2, 70.0) in the ruxolitinib arm and 39.4% (95% CI: 31.6, 47.5) in the BAT arm. There was a statistically significant difference between the treatment arms (stratified Cochrane- Mantel-Haenszel test p<0.0001, one-sided, odds ratio: 2.64 with 95% CI: 1.65, 4.22). The study also met the key secondary endpoint, with a statistically significant difference between two arms and in favor of ruxolitinib (39.6% in ruxolitinib arm and 21.9% in BAT arm; odds ratio: 2.38; 95% CI: 1.43, 3.94; p=0.0005).

The results observed in the adolescent patients are similar to the overall study population.

The overall safety profile of RUX-treated patients is consistent with its established safety profile and as expected in the study population. The safety profile of Jakavi is mainly characterised by cytopenias and infections. The safety profile of ruxolitinib in adolescents was similar to that of respective overall populations. No new safety concerns were identified in the present GvHD studies with ruxolitinib therapy.

It should be noticed that this study has been also submitted and assessed with an application for extension of indication for Jakavi (II-53) to include treatment of patients with GvHD aged 12 years and older who have inadequate response to corticosteroids or other systemic therapies. The assessment of the variation II-53 is still ongoing and any impact on the Product Information for study CINC424C2301 will be discussed in this parallel ongoing procedure.

3. CHMP overall conclusion and recommendation

Having considered data provided in the final clinical study report for the study CINC424C2301, the post authorisation measure is considered

☒ Fulfilled:

No regulatory action required.