2. SYNOPSIS

Name of Sponsor: Medical Center – University of Freiburg	Individual Trial Table Referring to Part <<insert part #>> of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Jakavi®	Volume:	
Name of Active Ingredient: Ruxolitinib	Page:	

Title of Study: Multicenter randomized Phase 2 trial to determine the Response Rate of Ruxolitinib and Best Available Treatment (BAT) versus BAT in Steroid-refractory acute Graft-versus-Host Disease (aGvHD).

Protocol no. RIG-P000814 and EudraCT no. 2014-004267-20.

Investigators:

Coordinating Investigator was Prof. Dr. Nikolas von Bubnoff.

The list of principal investigators of participated centres is provided in Appendix 16.1.4.

Study centre(s):

A total of 11 centres in Germany participated in this study and 8 centres enrolled patients.

Publication (reference):

BMC Cancer. 2018 Nov 19;18(1):1132. doi: 10.1186/s12885-018-5045-7

Study period (years):	**Phase of development**:
First patient in: 29 Jun 2017 Last patient out: 09 Oct 2019	Phase II

Objectives:

The primary objective was to evaluate the efficacy of Ruxolitinib/BAT as compared to BAT alone at day 28 after randomization.

The secondary objectives were:

Efficacy:

- Efficacy of Ruxolitinib/BAT as compared to BAT alone at day 14 after randomization
- Durable Overall Response Rate (ORR) persisting for at least 4 consecutive weeks within 8 weeks after randomization
- Time to treatment response
- Rate of patients with treatment failure
- Duration of response
- Overall Survival (OS)
- Event-free survival (EFS)
- Non Relapse Mortality (NRM)
- Failure-free survival (FFS)
- Steroid tapering failure rate
- Ruxolitinib discontinuation rate (≥ 4 weeks)
- Discontinuation rate of steroid therapy for GvHD
- Efficacy of Ruxolitinib after cross-over from BAT alone to Ruxolitinib/BAT at day 14 after cross-over
- Efficacy of Ruxolitinib after cross-over from BAT alone to Ruxolitinib/BAT at day 28 after cross-over
- Durable ORR persisting for at least 4 consecutive weeks within 8 weeks after cross-over
- Cumulative steroid dose until day 56
- Reduction of GvHD blood biomarker rate
- Relapse rate of underlying hematologic disease
- Graft failure rates
- Quality of life (QoL)
- Rates and severity of chronic GvHD over time

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Safety:

- Safety of Ruxolitinib treatment in GvHD
- Frequency of Cytomegalovirus (CMV) reactivation under therapy
- Duration of inpatient stay

Trial Hypotheses:

In this trial, we tested the hypothesis that therapeutic suppression of inflammatory cytokine signalling with Ruxolitinib is superior to BAT in steroid-refractory GvHD, as measured by the GvHD severity score. In addition, it was tested whether JAK1/2 inhibitor treatment allows to spare alternative GvHD agents, in particular the use of steroids, and whether JAK1/2 inhibition leads to suppression of inflammatory response as measured by plasma cytokines.

Methodology:

Open-label, multicenter, randomized phase II clinical trial conducted in a total of 11 investigational sites in Germany.

Number of patients (planned and analyzed):

Planned:	160
Screened:	24
Enrolled:	22 (11 Ruxolitinib/BAT, 11 BAT)
Randomized	21 (11 Ruxolitinib/BAT, 10 BAT)
Analyzed:	17 (10 Ruxolitinib/BAT, 7 BAT)

Diagnosis and main criteria for inclusion:

Steroid-refractory acute Graft-versus-Host Disease.

Main Criteria for inclusion:

- Acute skin, intestinal (histologically confirmed) or liver GvHD > grade 1 according to standard criteria [22]
- Age ≥18 years
- Failure of previous treatment, defined as presence of at least one of the following criteria:
  - Treatment with prednisone/prednisolone/methylprednisolone in a dose of at least 2 mg/kg and lack of response after at least 7 days treatment
  - Treatment with prednisone/prednisolone/methylprednisolone in a dose of at least 2 mg/kg and progression after at least 3 days of treatment
  - Failure to taper the prednisone/prednisolone dose to <0.6 mg/kg/day or methylprednisolone dose to <0.5 mg/kg/day
- Written informed consent
- Ability to understand the nature of the study and the study related procedures and to comply with them.

Main Criteria for exclusion:

- Uncontrolled underlying disease
- Active bleeding
- Absence of clinical signs of acute GvHD [22]
- Diagnostic or distinctive clinical signs of chronic GvHD [1]
- Uncontrolled bacterial, viral or fungal infection
- Absolute neutrophil count <0.5x103/µl
- Evidence of transplant-associated microangiopathy (TAM)# [23]

- Any previous JAK2 inhibitor treatment prior to study enrolment, except Ruxolitinib given prior to the allogeneic stem cell transplantation
- Known Hypersensitivity to Ruxolitinib or any of the excipients
- Known positivity for HIV, Hepatitis B or Hepatitis C at the time of screening.
- Female patients who are pregnant or breast feeding
- Concomitant use of any other investigational drug within the last thirty days before the start of this study.

According to Jodele et al., 2015 [23], diagnostic criteria for TAM.

Investigational Product, dose and mode of administration, batch number:

Treatment with BAT according to DGHO-Onkopedia guidelines for treatment of acute GvHD (as of March 2018). Treatment with Ruxolitinib at a dose of 10 mg BID orally in addition to BAT according to DGHO-Onkopedia guidelines.

A listing of used batch numbers is provided in Appendix 16.1.6.

Duration of Treatment:

Standard treatment: Treatment with BAT according to DGHO-Onkopedia guidelines for treatment of acute GvHD (as of March 2018). Optional cross-over from BAT alone to Ruxolitinib and BAT in case of lack of response from day 28 until day 56.

Experimental intervention: Treatment with Ruxolitinib at a dose of 10 mg BID orally addition to BAT according DGHO-Onkopedia guidelines.

Duration of intervention per patient: 6 months (could have been prolonged if patient experienced benefit from treatment).

Follow-up per patient: 12 months after end of treatment.

Criteria for evaluation:

Efficacy:

Primary endpoint:

Overall response rate (ORR) at day 28, defined as proportion of patients in each arm demonstrating partial response (PR) or complete response (CR) without requirement for additional systemic immunosuppressive therapy (IST) at day 28 after randomization, as compared to time of randomization (Visit 1, day 1).

Secondary endpoints:

ORR at day 14, defined as proportion of patients in each arm demonstrating PR or CR without requirement for additional systemic IST at day 14 after randomization.

Durable ORR, defined as proportion of patients in each arm achieving a CR or PR persisting for at least 4 consecutive weeks within 8 weeks after randomization.

Time to treatment response, defined as time from randomization to the date of first documentation of PR or CR. Death or relapse/progression of underlying hematologic disease without prior response was considered a competing event. Comparison of treatment arms was conducted until day 28 only, as cross-over to Ruxolitinib was offered to non-responders then.

Rate of patients with treatment failure, defined as rate of patients in each arm with treatment failure until day 28 after randomization.

Duration of response, assessed for responders only by calculating the time from first response to the date of first observation of aGvHD relapse/progression or the date of additional IST for GvHD. Onset of chronic GvHD or death without prior observation of aGvHD relapse or progression were

considered competing events, and observations where neither occurred were treated as censored observations.

Overall Survival (OS), defined as time from randomization to the date of death from any cause.

Event-free survival (EFS), defined as the time from randomization to the date of recurrence of underlying hematologic disease, graft failure or death due to any cause.

Non Relapse Mortality (NRM), defined as the time from randomization to the date of death not preceded by hematologic disease recurrence. Hematologic disease recurrence / progression was considered a competing event.

Failure-free survival (FFS), defined as the time from randomization to recurrence of underlying hematologic disease, graft failure, NRM or addition of new systemic IST for GvHD. Onset of cGvHD was considered a competing event.

Steroid tapering failure rate, defined as rate of patients in whom failure to taper steroids below methylprednisolone dose of 0.5 mg/kg/day (or equivalent <0.6 mg/kg/day of prednisone/ prednisolone) was observed within 56 days after randomization OR addition of any new IST for GvHD due to failure to taper steroids below methylprednisolone dose of 0.5 mg/kg/day (or equivalent <0.6 mg/kg/day of prednisone/prednisolone).

Ruxolitinib discontinuation rate, defined as rate of patients who discontinued Ruxolitinib treatment for at least 4 weeks.

Discontinuation rate of steroid therapy, defined as discontinuation rate of steroid therapy for GvHD for at least 4 weeks.

ORR after cross-over from BAT alone to Ruxolitinib/BAT at day 14 after cross-over, defined as proportion of patients demonstrating PR or CR without requirement for additional systemic IST at day 14 after date of cross-over from BAT alone to Ruxolitinib/BAT.

ORR after cross-over from BAT alone to Ruxolitinib/BAT at day 28 after cross-over, defined as proportion of patients demonstrating PR or CR without requirement for additional systemic IST at day 28 after date of cross-over from BAT alone to Ruxolitinib/BAT.

Durable ORR after cross-over, defined as proportion of patients who achieved a CR or PR without requirement for additional systemic IST, persisting for at least 4 consecutive weeks within 8 weeks after the date of cross-over from BAT only to Ruxolitinib/BAT.

Cumulative steroid dose until day 56.

Reduction of GvHD blood biomarker rate on day 8 after randomization.

Relapse rate of underlying hematologic disease: For the calculation of relapse incidence rates, time from randomization to the date of relapse diagnosis was calculated. Death without prior relapse was considered a competing event.

Graft failure rates: For the calculation of graft failure incidence rates, time from randomization to the date of graft failure diagnosis was calculated. Death without prior graft failure was considered a competing event.

Quality of life (QoL): For the assessment of the QoL, the EORTC QLQ-C30 and EORTC QLQ-C29 questionnaires were evaluated.

Rates and severity of cGvHD over time: Time from randomisation to the start date of any chronic GvHD. Hematologic relapse/progression and death without prior chronic GvHD were considered competing events.

Safety:

Secondary endpoints:

Safety of Ruxolitinib treatment in GvHD: Type, frequency, severity and relationship of adverse events (AEs) to investigational product, engraftment, infections.

Frequency of Cytomegalovirus (CMV) reactivation under therapy.

Duration of inpatient stay, calculated by the number of nights in hospital.

Changes in the conduct of the study:

The table below gives an overview about all submitted versions of the Clinical Trial Protocol (CTP) during the course of this study.

Procedure	**CTP version, dated**	**Ethics committee / BfArM**	**Date of vote / approval**
First submission:	V1.0, 09 Mar 2015	Ethic vote	Not approved; re-submission with regard to content: CTP V1.1
		BfArM approval	16.04.2015
Substantial Amendment:	V1.1, 20 Oct 2015	Ethic vote	24.11.2015
		BfArM approval	27.11.2015
Substantial Amendment:	V2.0, 01 Dec 2015	Ethic vote	05.02.2016
		BfArM approval	11.02.2016
Withdrawal of request:			02.05.2016
Resubmission:	V3.0, 31 May 2016	Ethic vote	Additional information requested was implemented in V3.1
		BfArM approval	01 Sep 2016
	V3.1, 01 Aug 2016	Ethic vote	08 Aug 2016
		BfArM approval	Implicit notice of receipt by 12 Sep 2016, as non-substantial
Substantial Amendment:	V4.0, 25 Apr 2017	Ethic vote	01.06.2017
		BfArM approval	26.05.2017
Substantial Amendment:	V5.0, 14 Sep 2018	Ethic vote	Submitted:13 Nov 2018
		BfArM approval	22 Nov 2018

Details of all modifications made are provided in section 9.8.1.

Statistical methods:

The statistical methods used are described in detail in the final version of the Statistical Analysis Plan (SAP), dated 29 January 2021 (see Appendix 16.1.9). All analyses were done using the Statistical Analysis System (SAS), Version 9.4.

The sample size calculation was based on the primary endpoint response (ORR). An expected proportion of 30% for the patients with best available treatment and an expected alternative proportion of 50% for the patients with acute GvHD treated with Ruxolitinib [24] was assumed. The alternative assumption was based on published data of 60 patients with acute and chronic GvHD treated with Ruxolitinib [25], and on recent papers for BAT [13, 26]. The study was planned to detect a response difference between treatment arms at a one-sided significance level α=5% with a power of 1-β=80%, when the response probabilities are 50% (Ruxolitinib) and 30% (standard treatment). Based on the χ^2 Test, 148 patients (74 per group) were planned to be included in the analysis (nQuery Advisor 7.0). A small number of drop-outs not evaluable for the intention-to-treat analysis of the primary endpoint may occur. Further missing response was to be evaluated as non-response according to the intention-to-treat principle. This might blur the assumed difference between treatment groups. Therefore we increased the calculated sample size by 8%, and 160 patients were planned to be randomised.

Efficacy analysis:

The primary objective was to evaluate the efficacy of Ruxolitinib and BAT as compared to BAT only measured as ORR at day 28. The null hypothesis was that the response probability for Ruxolitinib and BAT is below the response rate for BAT only, and the alternative hypothesis, that the response probability is higher for Ruxolitinib and BAT treatment than for BAT only (H_0: $p_0 \geq p_1$ vs H_1: $p_0<p_1$, where p_0, p_1 denote response probabilities for BAT only (p_0) versus Ruxolitinib and BAT (p_1)).

The primary analysis was based on the Full Analysis Set (FAS) and was conducted with a logistic regression model of the primary endpoint response to GvHD treatment as defined above. The model included treatment assignment (Ruxolitinib and BAT vs BAT only). In the CTP, adjustment for the stratification variables aGvHD grade (≤ grade 3 versus grade 4) and number of previous immunosuppressive treatments (≤ 3 versus ≥ 4) as covariates was planned, but could not be conducted due to low patient numbers in the strata as well as on total. The primary hypothesis was tested at a one sided level α=5% within this model. Odds ratios were calculated with two-sided 90% confidence intervals (CI), and the null hypothesis was to be rejected in favour of the alternative, if the lower bound of the CI for the odds ratio of Ruxolitinib and BAT compared to BAT only was above 1. The logistic regression models the probability of non-response.

Patients with missing response evaluation were counted as non-responders. Exact CI's based on the binomial distribution are presented for response rates in each treatment group. Additionally, two-sided 95% CI are reported in order to provide comparability with data from literature.

Binary secondary endpoints were estimated as rates in each treatment group. Relevant endpoints of this type (ORR at day 14, durable ORR persisting for at least 4 consecutive weeks within 8 weeks after randomization) are presented with exact two-sided 95% confidence intervals derived from the binomial distribution, and the same type of logistic model as for the primary endpoint was applied.

OS and EFS probabilities were estimated and displayed using the Kaplan Meier method.

The analysis of secondary time-to-event endpoints with competing risks was performed by means of the Aalen Johanson estimator for the calculation of cumulative incidence rates. Appropriate Regression models (Cox models for OS, EFS, Fine and Gray models for endpoints with competing events) were applied. If no competing events were observed, Kaplan Meier estimation and Cox regression could be applied for the respective endpoint. Time to treatment response and response duration are listed. The calculation of response duration was performed irrespective of treatment failure events due to additional IST or onset of chronic GvHD.

Cross-over to Ruxolitinib treatment after failure of BAT treatment was documented for one patient only. Therefore, no analysis of endpoints to be observed after cross-over was performed. All data are contained in the listings.

Safety analysis:

All safety parameters (AEs, laboratory assessments, vital signs) are listed by patient and summarized in total and by received treatment in the safety set (SAF).

All AEs are displayed in summary tables showing the total number of AEs, the minimum, maximum and mean number of AEs per patient, and the number of patients who had at least one AE is given. The incidence of AEs defined by MedDRA preferred term (PT) was calculated as the number of patients who experienced at least one AE with the respective PT in percentage of the total number of patients in the SAF. In the incidence tables the PTs were grouped by MedDRA system organ class (SOC) and high level term (HLT). Additionally, the incidence of AEs defined by SOC were calculated as the number of patients who experienced at least one AE in the respective SOC as percentage of the total number of patients in the SAF. Each incidence table was produced for the following AE sets: all AEs, AEs being at least severe, AEs possibly related to Ruxolitinib, and AEs possibly related to Ruxolitinib being at least severe.

Serious AEs (SAEs) were reported in the same way as the AEs. All deaths that occurred during the study, including the post treatment follow-up period, are listed for the SAF.

Laboratory data were listed in the measured units (or in SI units, being converted from the original units, if necessary). Values assessed as clinically relevant by the investigator are flagged in the listings. Vital signs and other observations related to safety are listed. For the EORTC questionnaires QLQ-C30 and QLQ-HDC29, scales were calculated according to EORTC scoring manuals (1, 2). Scales were summarized in total and by randomized treatment for each visit.

SUMMARY - CONCLUSIONS:

The present study "Multicenter, randomized Phase 2 Trial to determine the Response Rate of Ruxolitinib and Best Available Treatment (BAT) versus BAT in Steroid refractory acute Graft-versus-Host Disease (aGvHD)" was prematurely terminated on 15 November 2019 because, in view of the results of the randomized phase III study REACH2, a significant advantage for the test substance Ruxolitinib over BAT was reported (N Engl J Med. 2020 May 7; 382 (19): 1800-1810); Thus it was no longer justifiable to include patients in the BAT arm.

22 patients who met the inclusion criteria were informed and enrolled. One (1) patient was not randomized because he died after 9 days, 21 patients were randomized. Four patients did not start randomized treatment. In the Ruxolitinib arm, 1 patient was excluded from the FAS because he did not meet the inclusion criterion of treatment failure. In the BAT arm, 3 patients were excluded because the attending physician had decided to do so (2) and because of withdrawal of informed consent (1). A total of 17 patients were treated in the two arms, 10 of them in the Ruxolitinib arm and 7 in the BAT arm.

EFFICACY RESULTS:

The primary endpoint of the present study was the overall response rate on day 28. The frequency of the response, i.e. reaching a partial remission (PR) or complete remission (CR), was 50.0% (95%-CI: 18.7% to 81.3%) in the Ruxolitinib group and 57.1% (95%-CI: 18.4% to 90.1%) in the BAT group. The difference between the two treatment arms was statistically not significant (p=0.7717).

On day 14, the frequency of response was higher in the Ruxolitinib group, i.e. 50.0% compared to 28.6% in the BAT group (p=0.3823). The frequency of the response over a period of at least 4 weeks within an observation period of 8 weeks was 40.0% in the Ruxolitinib group and 57.1% in the BAT group (p=0.4882). Concerning the change of the acute GvHD overall grade in the course of the study, 5 patients in the Ruxolitinib arm and 3 patients in the BAT arm had acute GvHD of

grade III or IV at week 1, whereas at week 24 there was no patient in both treatment arms with such grading.

The time to event analyses yielded slightly better survival rates for the BAT group. For overall survival the Hazard ratio between the BAT and Ruxolitinib groups was 0.396 (95%-CI: 0.079 to 1.977). Regarding event-free survival, the Hazard ratio between BAT arm and Ruxolitinib arm was 0.291 (95%-CI: 0.059 to 1.425), For non-relapse mortality, the Hazard ratio was 0.388 (95%-CI: 0.100 to 1.515) with a p value for the difference between the two treatment arms of 0.1733.

SAFETY RESULTS:

Overall, 16 (94.1%) of the 17 patients in the SAF experienced at least one AE during the study. In total 164 events were reported, 111 in the Ruxolitinib arm and 53 in the BAT arm.

The most frequent AEs in the study were from MedDRA PTs 'Cytomegalovirus infection reactivation' (8 patients, 47.1%), 'pneumonia' and 'anaemia' (7 patients, 41.2%, each), 'oedema peripheral' (6 patients, 35.3%), 'thrombocytopenia' (5 patients, 29.4%), and 'platelet count decreased' (4 patients, 23.5%).

Eleven patients (64.7%), 8 in the Ruxolitinib arm and 3 in the BAT arm experienced at least one SAE during the study. In total 31 such events were reported, 20 in the Ruxolitinib arm and 11 in the BAT arm. The most frequently reported SAEs were from MedDRA PTs 'pneumonia' (6 patients, 35.3%), 'sepsis' (3 patients, 17.6%), and 'sinusitis' (2 patients, 11.8%). For 4 (40%) of the 10 patients of the Ruxolitinib arm at least one SAE being related to the study medication was documented. On a MedDRA PT level, the reported diagnoses were 'pneumonia' (2 patients, 11.8%), and 'Cytomegalovirus infection reactivation', 'sepsis' and 'pancytopenia' (1 patient, 5.9%, each).

Overall, 7 patients (6 in the Ruxolitinib arm and 1 in the BAT arm) experienced 10 (8 and 2, respectively) SAEs leading to death. Except for one case of pancytopenia, all other patients died from infections, i.e. from pneumonia, atypical pneumonia, sepsis, and/or septic shock. A total of 3 patients in the Ruxolitinib group died due to SAES possibly related to the study medication. The respective events were pneumonia, sepsis, and pancytopenia/pneumonia.

For nearly all reported AEs and SAEs, regardless of any relationship to the study medication, incidences were distinctly higher in the Ruxolitinib group as compared to the BAT group.

CONCLUSIONS:

Overall, the data are only partially meaningful because the number of recruited patients was too small for detailed statistical analyses due to the premature termination of the study.

Study sites:

- Universitätsklinikum Freiburg

Klinik für Innere Medizin I
Hämatologie, Onkologie und Stammzelltransplantation
Hugstetter Straße 55, 79106 Freiburg

- Universitätsklinikum Dresden

Medizinische Klinik und Poliklinik I
Fetscherstraße 74, 01307 Dresden

- Charité - Universitätsmedizin Berlin

CVK: Campus Virchow-Klinikum,
Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorimmunologie, CC 14: Tumormedizin
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- Universitätsklinikum Hamburg Eppendorf

Klinik und Poliklinik für Stammzelltransplantation
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- Universitätsklinikum Bonn

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Abteilung für Hämatologie und Onkologie
Sigmund-Freud-Straße 25, 53105 Bonn

- Universitätsklinikum Köln (AöR)

Klinik I für Innere Medizin
KMT-Ambulanz, BH Ebene 5
Kerpener Str. 62, 50937 Köln

- Universitätsklinikum Heidelberg

Medizin V , Hämatologie, Onkologie, Rheumatologie
Im Neuenheimer Feld 410, 69120 Heidelberg

- Universitätsklinikum München TU rechts der Isar

III. Medizinische Klinik und Polyklinik
Ismaninger Straße 22, 81675 München

- Universitätsklinikum Würzburg

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- Universitätsklinikum des Saarlandes

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Date of the Report: 07 December 2022