Synopsis: Clinical Study Report

Ruxolitinib versus allogeneic stem cell transplantation for patients with myelofibrosis according to donor availability: A prospective phase II trial (MMM 02 study)

Name of Investigational Product:	**Test-IMP: human allogeneic hematopoietic stem cells (allo-HSC)** **Comparator-IMP: Ruxolitinib**
Indication:	**Myelofibrosis**
Sponsor:	**University Medical Center Hamburg Eppendorf** **Martinistraße 52** **20246 Hamburg** **Germany**
Protocol Number:	**MMM 02 Study**
EudraCT Number:	**2014-005210-28**
Development Phase:	**Phase II**
Study Initiation Date:	**First Patient Consented: 09.01.2017**
Study Completion Date:	**Last Follow-up Visit: 07.10.2024**
Coordinating Investigator LKP (responsible until 31.03.2025, clinical study phase):	**Nicolaus Kröger** **Department of Stem Cell Transplantation** **University Medical Center Hamburg-Eppendorf** **Martinistraße 52** **20246 Hamburg, Germany**
Sponsor Investigator (responsible from 01.04.2025, analysis phase, CSR release)	**Dr. Nico Gagelmann** **Department of Stem Cell Transplantation** **University Medical Center Hamburg-Eppendorf** **Martinistraße 52** **20246 Hamburg, Germany**
Version/Date of Report:	**Final; 08-Oct-2025**

Synopsis

Name of Sponsor/Company: University Medical Center Hamburg Eppendorf	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Human allogeneic hematopoietic stem cells (allo-HSC)	**Volume:**	
Name of Active Ingredient: Human allogeneic hematopoietic stem cells (allo-HSC)	**Page:**	
Study Title	Ruxolitinib versus allogeneic stem cell transplantation for patients with myelofibrosis according to donor availability: A prospective phase II trial	
Protocol Number: **EudraCT Number:**	MMM 02 Study 2014-005210-28	
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Study Centers	14 German Study Centers in total: 01: University Medical Center Hamburg-Eppendorf (UKE) 02: Jena University Hospital 03: University Hospital Bonn (UKB) 05: Robert Bosch Hospital Stuttgart 06: University Medical Center of the Johannes Gutenberg University Mainz 07: University Hospital of Düsseldorf (UKD) 08: Johannes Wesling Hospital Minden 10: Hospital Nürnberg 12: University Medical Centre of Münster 14: University Hospital Tübingen 16: Helios Hospital Berlin Buch 19: University Hospital Ulm 21: University Hospital Aachen 22: University Hospital Halle (Saale)	
Publication (reference)	Not applicable	
Study Period.	09-JAN-2017 (First Patient In) 07-OCT-2024 (Last Patient Out)	
Phase of development	Phase II	

Objectives	**Primary objective** To compare efficacy in terms of event free survival of allogeneic stem cell transplantation (SCT) for patients with myelofibrosis who have a suitable stem cell donor after 3 months Ruxolitinib induction therapy with patients who lack a suitable stem cell donor and will continue to receive Ruxolitinib. **Secondary objectives** To assess and compare the safety and efficacy of study treatments/induction therapy in both study arms on spleen reduction, improvement of constitutional symptoms, Quality of life (QoL), toxicity, fibrosis regression, development of Graft vs Host Disease (GvHD) as well as chimerism, engraftment, relapse incidence, disease related mortality outcome and overall survival (OS).
Methodology	Open label, two arm, multicenter phase II trial. Treatment A: Allogeneic SCT after 3 months of Ruxolitinib induction therapy Treatment B: Ruxolitinib continuous therapy after 3 months of Ruxolitinib induction therapy
Number of subjects (planned and analyzed):	**Planned:** 155 patients were planned to be enrolled. (93 allogeneic SCT and 62 Ruxolitinib continuous therapy) **Analyzed:** 71 patients were analyzed within this study. Due to low recruitment, in protocol version 5.0 the following section was implemented: “If the planned number of 155 patients can't be enrolled in the study 12 months after implementation of Amendment 2, Version 5.0, recruitment will be stopped regardless of the actual patient number at that time. The whole study will end after the last follow-up visit of the last patient (i.e. anticipated in June 2024).”
Diagnosis and Main Criteria for Inclusion	1. Symptomatic primary myelofibrosis or myelofibrosis post polycythaemia vera or essential thrombocythemia stage intermediate 2- or high-risk according to International Prognostic Scoring System (IPSS) or dynamic IPSS (DIPSS) or intermediate 1-risk with high-risk cytogenetics, other than normal karyotype, sole del 20q, del 13q, or sole +9, or transfusion-dependency 2. Patients aged: 18 - 70 years at time of inclusion (female and male). 3. Patients understand and voluntarily sign an informed consent form. 4. Platelet count ≥ 50 x 10^9/L 5. Max. 6 weeks of Ruxolitinib treatment prior inclusion **6.** Eastern Cooperative Oncology Group (ECOG) ≤ 2
Main Criteria for Exclusion	1. Severe renal, hepatic, pulmonary or cardiac disease, such as: • Total bilirubin, serum Glutamic Oxaloacetic Transaminase (SGPT) or serum Glutamic Pyruvic Oxaloacetic Transaminase (SGOT) > 3 times upper the normal level • Left ventricular ejection fraction < 30 % • Creatinine clearance < 30 ml/min • Diffusing capacity of the lung for carbon monoxide (DLCO) < 35 % and/or receiving supplementary continuous oxygen

	2. Positive serology for human immunodeficiency virus (HIV) Pregnant or lactating women (positive serum pregnancy test) 3. Age < 18 and ≥ 71 years. 4. Uncontrolled invasive fungal infection at time of screening (baseline) 5. Serious psychiatric or psychological disorders 6. Participation in another study with ongoing use of unlicensed investigational product from 28 days before study enrollment 7. Transformation to acute myeloid leukemia (AML)
Test Product, Dose and Mode of Administration,	Test Product: Human allogeneic hematopoietic stem cells (allo-HSC) Mode of administration: Infusion Ruxolitinib: according to current SmPC
Duration of Treatment	Treatment Arm A: Allogeneic SCT after 3 months of Ruxolitinib induction therapy (SCT arm) Treatment Arm B: Ruxolitinib continuous therapy (36 month) after 3 months of Ruxolitinib induction therapy (ContRuxo arm)
Criteria for Evaluation	**Efficacy**: Primary Endpoint: 1. Event free survival (EFS) at 3 years after allogeneic SCT compared to Ruxolitinib continuous therapy in patients without a suitable donor Secondary Endpoints: 1. Overall survival at 3 years after allogeneic SCT compared to Ruxolitinib continuous therapy in patients without a suitable donor 2. Spleen reduction after 3 months Ruxolitinib induction therapy (the effect on spleen size will be analyzed according to the pretreatment versus no pretreatment of Ruxolitinib prior to study inclusion) 3. Improvement of constitutional symptoms (Loose of weight and night sweat) after 3 months Ruxolitinib induction therapy (the effect on constitutional symptoms will be analyzed according to the pretreatment versus no pretreatment of Ruxolitinib prior to study inclusion) 4. Improvement of bone marrow fibrosis after 3 months of Ruxolitinib induction therapy 5. Incidence of acute graft-versus-host disease on Day +100 after allogeneic SCT according to the Glucksberg scale revised by Przepiorka et al. 6. Incidence of chronic graft-versus-host disease according to the NIH consensus criteria of Filipovich et al. at 1, 2 and 3 years after allogeneic SCT 7. Toxicity of Ruxolitinib scored according to NCI CTCAE, Version 4.0 8. Toxicity of conditioning therapy scored according to NCI CTCAE, Version 4.0 9. Cumulative incidence of relapse at 3 years after allogeneic SCT 10. Disease-related mortality at 3 years after allogeneic SCT and Ruxolitinib continuous therapies 11. Non-relapsed mortality at 1 and 3 years after allogeneic SCT and Ruxolitinib continuous therapy

	12. Discontinuation rate at 3 years after Ruxolitinib continuous therapy (End of study) 13. Evaluation of Sorror Risk Score on outcome after allogeneic SCT 14. Impact of chimerism on relapse incidence after allogeneic SCT 15. Evaluation of bone marrow fibrosis regression after allogeneic SCT at 30 days, 100 days, 1 year, and 3 years 16. Evaluation of bone marrow fibrosis regression after Ruxolitinib continuous therapy at 30 days, 100 days, 1 year and 3 years 17. Evaluation of QoL (FACT-BMT) and QoL Myeloproliferated neoplasm (MPN) before Ruxolitinib induction therapy (= baseline), at transplantation, and after transplantation at 6 months, 1 year, 2 years and 3 years 18. Evaluation of QoL (FACT-BMT) and QOL (MPN-SAF-TSS) before Ruxolitinib induction therapy (= baseline), at confinement to Ruxolitinib continuous therapy and after confinement at 6 months, 1 year, 2 years and 3 years
Statistical Methods	The primary efficacy analysis was performed in the Full Analysis Set (FAS). 155 patients were planned to be enrolled. (93 allogeneic SCT and 62 Ruxolitinib continuous therapy) but due to low recruitment only 87 patients were recruited and 71 patients were analyzed within this study. The asymptotic Z-test was used to test for differences in the 3 year EFS rates measured by Kaplan-Meier method. Cox model, log-rank test and Kaplan-Meier survival analysis were used to determine the hazard ratio, p-values, risk estimates and related measures for time-to-event endpoints (event-free survival, overall survival). Descriptive summary statistics (mean, standard deviation, median, minimum and maximum, or absolute and relative frequencies) as well as descriptive p-values were provided for secondary outcome measures.
Efficacy Results	Seventy-one patients out of 87 recruited patients formed the full analysis set (FAS) in this trial. Of these, 83 patients were included in the study and 4 patients were screen failures. More males (68.7%) than females (31.3%) participated and the mean age was 58 years. According to the DIPPS score 9 patients (10.8%) were at high risk, 14 patients were at intermediate I risk (16.9%) and 51 patients had a risk scored as intermediate II (61.4%). Type of MF was mostly PMF (n=59, 71.1%); 14 patients had Post ET MF (16.9%) and 10 patients had Post PV (12%). The majority of patients had bone marrow fibrosis stage 2 or 3 (80.5%). The primary endpoint was event free survival (EFS) at 3 years after SCT compared to ContRuxo therapy in patients without a suitable donor. SCT showed significantly improved EFS at 3 years (74.4%) compared to ContRuxo (43.7%), with an absolute difference of 30.8% (p=0.048). The hazard ratio for EFS favored SCT accounting for age and DIPSS (HR 0.161; 95% CI: 0.057–0.457; p<0.001). Subgroup analyses confirmed consistent benefits of SCT across age and DIPSS risk groups.

	OS at 3 years was comparable (SCT 84%, ContRuxo 83%). Spleen responses were notable after ruxolitinib induction but did not differ significantly between arms thereafter. The median follow-up time was slightly shorter with 1176 days (range 169 – 1253 days) for the ContRuxo group and 1231 days (range 173 – 1439 days) for the SCT group. Weight increased significantly after 3 months of Ruxolitinib therapy and night sweats decreased in both treatment groups. Cumulative incidence (CI) of acute GvHD grade II-IV at 100 days after SCT was 23.8% (95% CI 16-39) and grade III/IV 7% (95% CI 2-15) while the CI of any chronic GvHD at 3 years was 63% (95% CI: 49-75) and of moderate/severe cGvHD 39% (95% CI: 26-52). Disease-related mortality was lower in the SCT arm (9% vs. 17%). Relapse/progression rates at 3 years were significantly higher in the ContRuxo group (56% vs. 18%, p=0.02), whereas NRM was higher in the SCT group (7% vs. 0%, p=0.04). Severe adverse events were more frequent with SCT (50%) compared to ContRuxo (31%), including infections, cytopenias, and GvHD. Ruxolitinib was mainly associated with hematological toxicities. The continuation rates at 3 years were quite similar with 71.4% in the SCT arm and 78.9% in the ContRuxo arm. When investigating the impact of comorbidity on event free survival the Hazard ratio was 0.289 (CI: 0.115; 0.726) for SCT and 1.391 (CI: 1.119; 1.729) for HCT-CI, meaning that the parameter HCT-CI has a significant impact on event free survival. Assessment of the grade of bone marrow fibrosis after allogeneic SCT showed that 100 days and 1 year after SCT the number of patients with grade 2 and 3 MF decreased and there were only patients with MF 0 and 1 at 3 years after SCT. However, a lot of data are missing, especially at 3 years (80.7%). The majority of data for this endpoint was also missing in the ContRuxo group, therefore, no conclusion can be drawn. Quality of life (QoL) initially declined following SCT but improved substantially over time, with a 45% reduction in symptom burden and an 8% increase in overall well-being (FACT-BMT) by 24 months. In contrast, QoL in the ContRuxo group remained more stable, with only modest symptom relief (22% reduction) and a 5% decline in functional QoL. <u>Further endpoints:</u> Neutrophils engraftment failed at 28 days after SCT in 11.1% of patients. Response to treatment ContRuxo group (N=14): After 3 months of induction stable disease (SD) was seen in 6 patients (42.9%); 5 patients (35.7%) showed clinical improvement (CI) and 1 patient each showed partial remission (PR), symptoms response or progressive disease. There were only a few patients available for evaluation after 1, 2 and 3 years of confinement, however, in the remaining patients after 36 months of confinement PR was seen in 2 patients (14.3%); 1 patient each showed CI or SD. Response to treatment SCT group (N=57): After 3 months of induction stable disease (SD) was seen in 32 patients (56.1%); 21 patients (36.8%) showed clinical improvement (CI) and

	2 patients each showed complete (CR) or partial remission (PR). At SCT day + 36 months CR was seen in 26 patients (45.6%); PR was seen in 5 patients (8.8%); CI was seen in 6 patients (10.5%); 2 patients relapsed, and 1 patient each showed symptoms response or SD. Subgroup analysis: The impact of age, gender and type of MF on event free survival and overall survival was evaluated. **Event free survival**: In the SCT arm age seems to have an impact on event-free survival since in this group the ratio was 93.8%, CI 47.5%; 82.6% (≤ 55 years) vs 66.3%, CI 52.8%; 83.1% (> 55 years). This effect was less pronounced in the ContRuxo group. Stratification by gender showed a big difference between males and females within the ContRuxo group with a survival function estimate of event free survival at 3 years of 0.000, (females) vs 50.0% (males). In contrast, the risk for events was quite similar in the SCT group. The type of MF seems to have an impact on event free survival since patients with a primary MF seems to be at higher risk for events compared to patients with a Post Essential Thrombocythemia MF or Post Polycythemia Vera MF. The ratio of event free survival at 3 years was 29.6%, CI 19.3%; 94.0% (PMF) vs 60.0%, CI 29.3%; 100.0% (Post ET MF, Post PV MF) in the ContRuxo group. **Overall survival**: Age seems to have some impact on overall survival since in both groups overall survival was a little better in the subgroup ≤55 years. The survival function estimate of overall survival at 3 years was 1.000 (≤ 55 years) vs 71.4%, (> 55 years) in the ContRuxo group and 93.8% (≤ 55 years) vs 79.4% (> 55 years) in the SCT group. The impact of gender on overall survival was quite small within both groups. The type of MF seems to have no impact on overall survival; treatments were not different in the MF classifications (primary MF,Post Essential Thrombocythemia MF or Post Polycythemia Vera MF).
Safety Results	Overall, 83 patients participated in this trial and out of those a total of 76 patients (91.6%) experienced any AE. Those were 13 patients (81.2%) in the ContRuxo arm, 60 patients (93.8%) in the SCT arm and all three patients that were not assigned to a treatment group. A total of 17 patients (20.5%) had a Ruxolitinib-related AE. Most AEs were noted in the SOC 'Blood and lymphatic system disorders' (n=8) followed by the SOC 'investigations' (n=5). Looking at PTs the AEs that occurred most frequently were anemia (n=4) and platelet count decreased (n=4). Most related AEs were noted in the SOC 'General disorders and administration site conditions' (n=17) followed by the SOCs 'infections and infestations (n=12) and 'investigations' (n=8). Looking at PTs the AE that occurred most frequently was mucosal inflammation (n=7).

	SCT-related AEs were seen in 23 patients (35.9%) and HSC-related AEs were present in 11 patients (17.2%). Most related AEs were noted in the SOC 'General disorders and administration site conditions' (n=17) followed by the SOCs 'infections and infestations (n=12) and 'investigations' (n=8). Looking at PTs the AE that occurred most frequently was mucosal inflammation (n=7). A total of 7 patients had AEs leading to a discontinuation of the trial intervention. Over the whole course of the study (including induction period), serious AEs were recorded in a total of 39 patients (47.0%), those were 5 patients (31.2%) in the Ruxolitinib-group, 32 patients (50.0%) in the SCT group and 2 patients not assigned to a treatment group. Eye infection, pneumonia, infection due to tuberculosis, and fever of unknown origin were considered as related to Ruxolitinib Febrile neutropenia, chronic GvHD, and poor engraftment were considered as related to allo-HSC or SCT. Ten patients died due to an SAE (15.6%); these were all assigned to the SCT arm. Only one of these SAEs was related to the treatment (poor engraftment). The most frequently occurring cause of death was progression of the underlying disease. Due to the nature of the disease the most frequently occurring abnormal and clinically significant abnormalities were noted related to hematological parameters. In both treatment groups hematological abnormalities normalized during the course of treatment. Regarding clinical chemistry there were mostly only very few parameters in single patients that were assessed as abnormal and clinically significant at single timepoints in both treatment groups. Regarding vital signs, physical findings, and ECOG performance status no remarkable changes were seen throughout the study. Weight was the parameter that fluctuated most during the course of the study.
Conclusion	This study demonstrates that SCT following ruxolitinib induction significantly improves EFS and disease control compared to continued ruxolitinib in patients with intermediate and high risk myelofibrosis (MF). Despite a relatively low NRM of 7%, SCT remains associated with substantial risks, including GvHD and other toxicities, underscoring the need for careful patient selection. Ruxolitinib remains valuable for symptom management and can serve as an effective bridge to transplant. These findings support SCT as the preferred curative approach for eligible MF patients and highlight the importance of strategies to mitigate transplant-related morbidity.
Date of Report	08-Oct-2025