SYNOPSIS

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Title of Study:

Prospective validation of a predictive model of response to romiplostim in patients with IPSS low or intermediate-1 risk myelodysplastic syndrome (MDS) and thrombocytopenia – the EUROPE trial

Substantial protocol changes:

The study was conducted according to the Clinical Study Protocol version 3.0 dated 05 Mar 2015 and the following amendments:

- Version 4.0 dated 20 May 2015: included minor specifications of the AML progression, HI-N response definition and extension of the screening period
- Version 5.0 dated 10 Jun 2017: included specification of visit assessments, statistical distributions of patients in the strata and instructions for reconstitution of the study drug
- Version 6.0 dated 30 Aug 2019: re-calculation of sample size due to poor recruitment in two of the three study arms, update of addresses and contact information

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Publication (reference)

Platzbecker U, Kubasch AS, Giagounidis A, et al. Biomarkers of response to romiplostim in patients with lower-risk myelodysplastic syndrome (MDS) and thrombocytopenia – results of the EUROPE trial by the EMSCO network. *Blood* 2019; 134 (Suppl 1): 2998.

Kubasch AS, Giagounidis A, Metzgeroth G, et al. A molecular-based response prediction model to romiplostim in patients with lower-risk MDS and severe thrombocytopenia. *Blood* 2020; 136 (Suppl 1): 44-45.

Kubasch AS, Giagounidis A, Metzgeroth G, et al. Prospective Validation of a Biomarker-Driven Response Prediction Model to Romiplostim in Lower-Risk Myelodysplastic Syndromes – Results of the EUROPE Trial by EMSCO *In preparation, submission to Leukemia planned for 04/2022*

Studied period (years):	6	**Phase of development:**
date of first enrolment:	21 May 2015	Phase II
date of last completed:	01 Jul 2021	

Objectives:

Primary: to investigate prospectively whether the current thrombopoietin (TPO) level based response model can predict response to romiplostim in thrombocytopenic patients with international prognostic scoring system (IPSS) low/int-1 MDS

Secondary: Safety, bleeding events, acute myeloid leukemia (AML) evolution, peripheral blasts during therapy, identification of molecular parameters associated with response and progression

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Methodology:

The study consisted of a screening period, a treatment period of max 4 months which was extended to a total of 1 year for patients identified as responders, and a 12-months follow-up period for all study participants. During the study, efficacy as well as safety and tolerability of the study medication were investigated.

Number of patients (planned and analysed):

Planned: at least 80 screened for a total enrollment of 75 patients

Analysed: 77 in the Full Analysis Set (FAS), 51 and 39 in the Per-Protocol Set (PPS) for the first and second treatment period, respectively

Diagnosis and main criteria for inclusion:

Male and female patients at an age of 18 or older diagnosed with IPSS low and int-1 MDS with thrombocytopenia

Test product product, dose and mode of administration, batch number:

Active ingredient: Romiplostim

Name of finished product: Nplate® 500 µg powder for solution for injection

Dose, route of administration and duration of treatment: Starting dose 750 µg once a week (7d ± 2d), subcutaneous injection, 4 months maximum duration for non-responders, for responders treatment period was extended for up to 1 year (8 months extension period). The dose was adjusted based on the subject's platelet count.

Batch numbers: 1055969, 1066887, 1073336, 1077714, 1081835, 1088132, 1099012

Marketing authorization number(s): EU/1/08/497/002

Duration of treatment:

During the first 16 weeks of treatment, 27 patients (35%) consistently received the full romiplostim dose of 750 µg without need for dose reduction. In 6 patients (7.8%), dose was adapted to 500 µg and in 1 patient (1.3%) to 125 µg. In 43 patients (55.8%), treatment was temporarily stopped for multiple reasons and later on reinitiated. In the second treatment period (Week 16 to Week 52) 8 patients (10.4%) consistently received the full dose, in 3 patients (3.9%) the dose was reduced to 250 µg and in 66 patients (85.7%) dosing was stopped. The median duration of treatment exposure was 145 days (range 12 - 576 days).

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Reference therapy, dose and mode of administration, batch number:

N/A

Criteria for evaluation:

Primary endpoint:

- Hematologic improvement of platelets (HI-P) after 4 months on therapy

Safety:

- Cumulative hematologic improvement of platelets (HI-P), erythrocytes (HI-E) and neutrophils (HI-N)
- Incidence of disease progression to higher stage MDS or AML
- Increase of peripheral blasts during therapy
- Association of the presence of certain mutations with disease progression in a retrospective analysis
- Incidence of bleeding events
- Type, incidence and severity of all adverse events (AEs) including clinically significant changes in laboratory values

Statistical methods:

All statistical analyses followed the procedures specified in the Clinical Study Protocol (Version 6.0, dated 30 Aug 2019) and the Statistical Analysis Plan (Version 1.0, dated 06 Jul 2020).

Summary statistics are presented for the total number of patients and by model groups. All continuous variables are summarized using the following statistics: n (non-missing sample size), number of missing values (Missing), arithmetic mean (Mean), standard deviation, (STD), median (Median), maximum (Max) and minimum (Min) and 95%-confidence interval (CI) for the mean.

All hypothesis were tested against two-sided alternatives. Only hypotheses concerning the comparison of model groups with respect to response rates were tested against one-sided alternatives. The level of significance was set to 5%.

If not stated otherwise, all analyses are based on FAS and PPS and the following test procedures were applied:

Categorical variables with two categories were analyzed using Fisher's exact test to compare proportions between model groups. Variables with more than two categories were compared by Pearson's Chi-square test. Additionally, contingency coefficient c_{corr} was calculated.

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Continuous variables were analyzed by the following procedure:
The Shapiro-Wilk Test was applied in order to check the hypothesis of normality distribution. In case of non-rejection of the normality hypothesis the model groups were compared by an analysis of covariance (ANCOVA) procedure which includes "group" as fixed effect and the baseline values as covariate. Estimates of effects, 95%-confidence limits and p-values were calculated.

If the hypothesis of normally distributed data was rejected, the ANCOVA procedure was based on Blom transformed ranks.

Comparisons to baseline by treatment group were performed as paired t-tests. In case of non-normal data Wilcoxons signed rank test based on intra-individual differences was applied.

Sensitivity analysis were optionally be performed for continuous variables by including the grouping/stratification variables in an ANCOVA model to estimate the impact and possibly correct treatment effects:

For categorical variables a logistic regression was performed including the specified effects as factors. Estimates of effects/odd ratios (OR) in the regression model, 95%-confidence limits and p-values were calculated.

The statistical model was consecutively reduced by the non-significant effect with the highest p-value until the model contained only significant effects besides the model group effect.

Summary – Conclusions:

Efficacy Results:

The primary efficacy endpoint was the rate of hematologic improvement of platelets (HI-P) defined as an absolute increase of platelet count to ≥ 30/nL for patients starting at > 20/nL or an increase of platelets from < 20/nL to > 20/nL and by at least 100%, according to International Working group (IWG) 2006 criteria lasting for ≥ 8 weeks after at least 16 Weeks of romiplostim treatment.

In general, there was an increase in platelets observed during treatment with romiplostim which was more pronounced in Group A as compared to Group B+C. The median peak increase in platelet count for responders was higher in Group A than in Group B+C (FAS Group A: 291 /nL [95% CI 250 - 491]; Group B+C: 108 /nL [95% CI -30.2 - 662]) and time to first peak increase was substantially shorter (FAS Group A: 34.0 days [95% CI 33.8 – 113]; Group B+C: 287 days [95% CI 134 - 353]).

Among the FAS population 32 patients were HI-P responders at Week 16, 24 in Group A and 8 in Group B+C. In the PPS, a total of 29 patients showed HI-P response with 21 in Group A and 8 in Group B+C. A statistically significant difference was observed in the frequency of responders between Group A and Group B+C (p< 0.001). Further, the duration of HI-P was significantly longer for patients in Group A (median 351 days [95% CI 349 - 352]) than in Group B+C (median 315 days [95% CI 292 - 338]); p=0.006.

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Model prediction

According to a previously published model of response to thrombopoietin receptor agonist (TPO-RA), patients were assigned into two different cohorts at the time of screening based on previous PTE and centrally assessed TPO serum levels (Group A: TPO < 500 ng/L and PTE < 6 units/past year; Group B+C: TPO > 500 ng/L, and/or PTE ≥ 6 units/past year).

Applying data derived from the present study, the predicted model was not confirmed, neither for FAS nor PPS.

Based on data from this study a new response prediction model was developed where the *SRSF2* mutation status and Hb level at baseline were significantly linked to HI-P, which achieved an overall accuracy of 70% for a correct romiplostim response prediction. The presence of an *SRSF2* mutation was identified as a significant predictor of response to romiplostim treatment (p=0.016, logistic regression). In patients with an *SRSF2* mutation, the probability to achieve HI-P was 65% compared to 33% in patients with *SRSF2* wildtype. Comparing responders versus non-responders, no significant changes were found of variant allelic burden of variants detected pre- and post-romiplostim treatment, which underlines the safety of romiplostim in this therapeutic setting and no expansion or stimulation of malignant clones.

Safety Results:

Hematologic improvement of neutrophils (HI-N)

Neutrophil response was only regarded for patients with pretreatment level < 1.0 /nL. Of these, only 3 patients allocated to Group A achieved HI-N and continued treatment after Week 16. The median peak increase in neutrophil count for responders in the FAS was 8.58 /nL [95% CI 6.51 – 10.2] and the median time to peak increase was 99.0 days [95% CI -149 - 430]. Median duration of HI-N response in Group A was 62 days [95% CI 50.8 – 73.2]. No HI-N was observed in Group B+C. None of the patients achieved HI-N after Week 16.

Hematologic improvement of erythrocytes (HI-E)

HI-E response was only regarded for patients with pretreatment hemoglobin (Hb) level < 11 g/dL who received less than four units of red blood cells (RBCs) within 8 weeks of cycle 1 day 1 (including patients not transfused).

In general, there was an increase in Hb observed during treatment with romiplostim which was less pronounced in Group A as compared to Group B+C. Among the FAS population 7 patients were HI-E responders at Week 16, 1 in Group A and 6 in Group B+C. At EOS the number of responders in Group B+C had increased to 12. Thus, at end of study the proportion of patients who achieved HI-E was significantly larger in Group B+C compared to Group A.

The median peak increase in Hb for responders was higher in Group A than in Group B+C (FAS Group A: 6.05 g/dL [95% CI n.a.]; Group B+C: 3.25 g/dL [95% CI 2.00 – 5.20]) and time to first peak increase was longer (FAS Group A: 217 days [95% CI n.a.]; Group B+C: 194 days [95% CI 134 - 285]). However, it has to be noted that Group A includes 1 responder only. The duration of response was not significantly different between the groups.

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Cumulative rate of hematologic improvement
None of the patients achieved simultaneous response of HI-P, HI-E and HI-N.

Disease progression
In the FAS, disease progression was reported for 10% of patients until end of study (EOS) and 25% until end of follow-up (FU). Progression free survival was not significantly different between the model groups.

Association of the presence of certain mutations with disease progression
Mutations were analyzed in 75 of 77 patients. There was no statistically significant difference observed in counts of mutations between HI-P responders and non-responders. A weak correlation was found between the presence of ASXL1 and disease progression.

Increase of peripheral blasts during therapy
The increase over time in peripheral blasts was significantly higher in Group A than in Group B+C (FAS p=0.001, PPS p=0.018).

Bleeding events
In total, 221 bleeding events were reported in the first treatment period until Week 16, 158 events in Group A and 63 events in Group B+C. From Week 20 through Week 52, a total of 64 events were documented, 49 in Group A and 15 in Group B+C. Most of the events were Grade 1.

Safety endpoints
A total of 658 treatment-emergent AEs (TEAEs) were recorded in 70 patients (91%), i.e. 499 events in 49 patients of Group A (96%) and 159 events in 21 patients of Group B+C (81%).
Overall, 99 out of the 658 TEAEs (15%) were assessed as likely or possibly related to the study medication romiplostim. The most frequent drug-related TEAEs were leukocytosis (7 patients, 9.1%), blast cells present/increased (6 patients, 7.8%), hematoma (4 patients, 5.2%), anemia (3 patients, 3.9%) and arthralgia (3 patients, 3.9%).
A total of 35 SAEs were documented in 20 patients (26%), 23 events in 12 patients of Group A (24%) and 12 events in 8 patients of Group B+C (31%). Seven patients (9%) experienced a serious adverse event (SAE) that was assessed as related to the study medication including AML (2 cases), asthenia, mucosal hemorrhage, drug-specific antibody, monocyte count increased, viral rash, cerebrovascular accident and pulmonary embolism (1 case each).
During treatment, 6 patients (7.8%) had transient appearance of centrally assessed peripheral blasts to >10%, which was reversible after romiplostim interruption and 2 patients (2.6%) progressed to AML. Thirteen patients (17%) had Grade 2 or higher bleeding events.
Except for leukocytosis, monocytosis and increase of peripheral blasts, no significant trends or general changes in safety laboratory parameters were observed that might be caused by the study medication romiplostim. One TEAE of hyperkalemia was documented and assessed as related to the study medication. One event of increased C-reactive protein was reported as SAE and assessed as not related to the study medication.

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No trends or general changes in vital parameters were observed during treatment with romiplostim. The following TEAEs were reported as possibly related to the study medication romiplostim: weight decreased 1 event, hypertension 5 events. No SAE was reported.
During study treatment one patient died from a thrombocytopenia that was assessed as not related to the study medication romiplostim. Twelve cases of death were documented during the follow-up period.

Conclusion:

Thirty-two patients (41.6%) achieved hematologic improvement of platelets (HI-P), while neutrophil (HI-N) and erythroid (HI-E) response were observed in 3 (3.9%) and 7 (9.1%) patients. Results confirm and extend observations of previous studies showing a high clinical efficacy in a large subset of patients. The median duration of response with 351 days in Group A and 315 days in Group B+C is encouraging, particularly considering that 31% of included patients were relapsed or refractory to at least one prior treatment line.

Results from this study could not confirm previous reports that platelet response significantly correlated with baseline endogenous TPO levels and platelet transfusion history. Based on data from this study a new response prediction model was developed where the *SRSF2* mutation status and Hb level at baseline were significantly linked to HI-P, which achieved an overall accuracy of 70% for a correct romiplostim response prediction. The presence of an *SRSF2* mutation was identified as a significant predictor of response to romiplostim treatment (p=0.016, logistic regression). In patients with an *SRSF2* mutation, the probability to achieve HI-P was 65% compared to 33% in patients with *SRSF2* wildtype. Interestingly, comparing responders vs. non-responders, no significant changes were found of variant allelic burden of variants detected pre- and post-romiplostim treatment, which underlines the safety of romiplostim in this therapeutic setting and no expansion or stimulation of malignant clones.

In conclusion, this prospective study did not confirm the predictive value of TPO levels and PTE on the response to romiplostim in patients with LR-MDS. Nevertheless, romiplostim is safe and highly efficacious in a large subset of patients. Further prospective and controlled studies are warranted to specify the definitive role of TPO-RA in the treatment landscape of LR-MDS. The newly developed response prediction model including *SRSF2* mutation status may help identifying patients with the highest likelihood of response also in future clinical trials. To avoid overfitting of variables and to confirm the results, the new response prediction model needs to be validated in an external independent cohort.

In summary, the study confirms the safety and efficacy of romiplostim in LR-MDS patients and may allow to better define subgroups of patients with a high likelihood of response.