# CLINICAL STUDY REPORT

## EFFICACY AND SAFETY OF ELTROMBOPAG IN PATIENTS WITH ACQUIRED MODERATE APLASTIC ANEMIA (EMAA) WHO ARE TREATED WITH CICLOSPORIN A

## PROSPECTIVE RANDOMIZED MULTICENTER STUDY COMPARING THROMBOPOETIN-RECEPTOR AGONIST ELTROMBOPAG WITH PLACEBO IN PATIENTS WITH ACQUIRED MODERATE APLASTIC ANEMIA WHO ARE TREATED WITH CICLOSPORIN A

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| **EudraCT number:** | 2014-000174-19 |
| **NCT number:** | NCT02773225 |
| **Protocol code:** | EMAA study / 9345 |
| **Name of the IMP:** | Eltrombopag |
| **Phase:** | Phase II - III |
| **Indication:** | Moderate aplastic anemia (MAA) |
| **Study dates:** | First patient first visit 27 May 2015<br>Last patient last visit 23 Dec 2024 |
| **Sponsor:** | University Hospital of Ulm<br>University of Ulm, Medical Faculty<br>Albert-Einstein-Allee 29<br>89081 Ulm, Germany |
| **Coordinating Investigator:** | Dr. Britta Höchsmann<br>Institute of Transfusion Medicine, University of Ulm<br>Helmholtzstrasse 10<br>89081 Ulm, Germany |
| **Version of the report** | 1.0 |
| **Date of the report:** | 27 Jul 2025 |

# 1 Signatures

The undersigned authors agree to the contents of this clinical study report by their signatures. The reported clinical trial was conducted according to the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and applicable laws.

Coordinating Investigator

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| Dr. Britta Höchsmann | Place, date |

Sponsor

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| Prof. Dr. Udo X. Kaisers, CMO | Place, date |

CRO

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| CEO, GWT-TUD GmbH<br>Prof. Dr. habil Jacques Rohayem | Place, date |

# 2 Synopsis

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| Date of Report | 27 Jul 2025 |
| Title of the study | Efficacy and Safety of Eltrombopag in Patients with Acquired Moderate Aplastic Anemia (EMAA) who are treated with Ciclosporin A<br>Prospective Randomized Multicenter Study comparing Thrombopoetin-Receptor agonist Eltrombopag with Placebo in Patients with Acquired Moderate Aplastic Anemia who are treated with Ciclosporin A |
| EudraCT number | 2014-000174-19 |
| NCT number | NCT02773225 |
| Sponsor | University Hospital of Ulm<br>Albert-Einstein-Allee 29<br>89081 Ulm, Germany |
| Phase | II - III |
| Indication | Moderate aplastic anemia (MAA) |
| Study objectives | **Primary objective**<br>The primary objective of this trial was the evaluation of the superiority of eltrombopag on top of background treatment with ciclosporin A (CSA) regarding hematologic response (partial response [PR] + complete response [CR]) at 6 months in comparison to treatment with CSA alone in untreated MAA patients.<br>**Secondary objectives**<br>The secondary objectives of this trial were to investigate the impact of eltrombopag added to background therapy with CSA on all outcome measures, safety and quality of life (QoL) in untreated MAA patients as well as the evaluation of telomere lengths and telomerase mutations as biomarkers for response to eltrombopag therapy in MAA, and the evaluation of the new Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria (PNH) specific QoL questionnaire QLQ-AA/PNH. |
| Study treatment (IMP) | Eltrombopag or placebo |
| Test product/active ingredient | Revolade® / Eltrombopag |
| Dose, route of administration and duration of treatment | Starting dose of 150 mg orally as 75 mg tablets once daily (i.e., 2 tablets á 75 mg per day) for 6 months, option of dose escalation to 225 mg per day after 6 months, maximum treatment duration 12 months with slow tapering over an additional period of 2 months |
| Batch numbers | 062015, 032020, 062020, 082020, 092020, 112020, 122020, 042021, 052021, 022022, 122022, 012023, 042023, 052023, 03F2022, 04F2021, 05F2021, 11F2020, 07S2017, 03S2020, 08S2020, 09S2020, 11S2020, 12S2020, 01S2023, SKU #763124, SKU #763124 |
| Marketing authorization number(s) | EU/1/10/612/013 |
| Name of finished product | Revolade® 75 mg film-coated tablets |
| Diagnosis and main criteria for inclusion | Male and female patients aged ≥18 years and diagnosed with MAA requiring standard treatment with CSA without prior specific therapy |

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| Study design | International, multicenter, randomized, placebo-controlled, double-blind, prospective clinical trial |
| Methodology | The study consisted of a screening period, a treatment period of 6 months with placebo or eltrombopag, and allocation to further treatment with eltrombopag depending on the response assessment after the initial 6 months of therapy. Patients were followed for 24 months after start of therapy or until the end of the study whatever occurred first. During the study, efficacy as well as safety and tolerability of the study medication were investigated. |
| Coordinating Investigator | Dr. Britta Höchsmann<br>Institute of Transfusion Medicine, University of Ulm<br>Helmholtzstrasse<br>89081 Ulm, Germany |
| CRO | GWT-TUD GmbH<br>Freiberger Strasse 33<br>01067 Dresden, Germany |
| Study centers and investigators | University of Ulm<br>Institute of Transfusion Medicine,<br>Helmholtzstraße 10<br>89081 Ulm, Germany — Dr. Britta Höchsmann; Prof. Dr. Hubert Schrezenmeier<br><br>Universitätsklinikum Aachen<br>Klinik für Onkologie, Hämatologie und Stammzelltransplantation<br>Pauwelstraße 30<br>52074 Aachen, Germany — Prof. Dr. Tim Brümmendorf; PD Dr. Fabian Beier<br><br>Medizinische Hochschule Hannover<br>Klinik für Hämatologie<br>Carl-Neuberg- Straße 1<br>30625 Hannover, Germany — Prof. Dr. Michael Heuser; Prof. Dr. Florian Heidel; Prof. Dr. Felicitas Thol<br><br>Universitätsklinikum Essen<br>Klinik für Hämatologie<br>Hufelandstraße 55<br>45147 Essen, Germany — Prof. Dr. Alexander Röth; PD Dr. Ferras Alashkar<br><br>Charité - Universitätsmedizin Berlin-Virchow Klinikum<br>Hämatologie, Onkologie, Tumorimmunologie<br>Augustenburger Platz 1, Ostring 4<br>13353 Berlin, Germany — Prof. Dr. Jörg Westermann; Dr. Michaela Schwarz<br><br>University Clinic Hamburg Eppendorf<br>Department of Oncology and Hematology<br>Martinistraße 52<br>20246 Hamburg, Germany — Dr. Philippe Schafhausen; Dr. Anne Marie Asemissen<br><br>Saint Louis Hospital<br>MT unit, Hematology Department<br>1 avenue Claude Vellefaux<br>75010 Paris, France — Prof. Dr. Régis Peffault de Latour; Dr. Flore Sicre de Fontbrune |

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| | Universitätsspital Basel<br>Hämatologie<br>Petersgraben 4<br>4031 Basel, Switzerland<br><br>Klinikum Chemnitz GmbH<br>Klinik für Innere Medizin III<br>Bürgerstraße 2<br>09113 Chemnitz, Germany | PD Dr. Dominik Heim<br>Dr. med. Beatrice Drexler<br>Dr. Jakob Passweg<br>PD Dr. Mathias Hänel<br>Dr. Regina Herbst |
| Study period | First patient first visit (FPFV) 27 May 2015<br>Last patient first visit (LPFV) 09 May 2023<br>Last patient last visit (LPLV) 23 Dec 2024<br>Database lock (DBL) 08 Jan 2025 | |
| Early termination | Not applicable | |
| Number of patients | Planned: 90 (45 per treatment group)<br>Analyzed: 85 in the full analysis set (FAS)<br>77 in the safety analysis set (SAF)<br>75 in the per-protocol set (PPS) | |
| Criteria for evaluation | **Primary endpoint**<br>The primary endpoint of the study was the hematologic response rate (CR + PR) at 6 months.<br>**Secondary endpoints**<br>• Trilineage (CR and PR) and single lineage hematological response rate at 3, 6, 12 and 18 months<br>• Cumulative incidence of response<br>• Time to best hematological trilineage and single lineage response<br>• Proportion of patients with need for transfusions and number of units transfused (packed red blood cells [pRBC] and platelet concentrate [PC]) since start of treatment<br>• Cumulative incidence of progress to severe aplastic anemia /very severe aplastic anemia (SAA/VSAA) or intensive immunosuppressive treatment with antithymocyte globulin (ATG)<br>• Toxicity profile as measured using the Common Terminology Criteria for Adverse Events (CTCAE)<br>• Relapse rate at 6, 12 and 18 months<br>• Cumulative incidence of relapse (from best trilineage hematological response)<br>• Overall survival (OS)<br>• Failure-free survival (FFS)<br>• Telomere lengths and presence of telomerase mutations as biomarkers for response<br>• Quality of life (QoL) as assessed by QoL instruments (FACIT-F SCALE and EORTC QLQ-C30, QLQ-AA/PNH)<br>**Exploratory endpoints**<br>• Pharmacokinetic studies for assessment of dose dependency regarding efficiency and safety in a subgroup of patients (not evaluated) | |
| Statistical methods | All statistical analyses followed the procedures specified in the Clinical Study Protocol (version 6.0, dated 09 Oct 2024) and the Statistical Analysis Plan (SAP) (version 1.0, dated 08 Jan 2025). | |

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| | Baseline response (PR+CR) expectation after 6 months with standard immunosuppression with CSA alone was 46% [1].<br>The sample size was calculated on the hypothesis that in the experimental arm the addition of eltrombopag increases the 6-months response rate (CR + PR) up to 71%. In these conditions, for a targeted power of 80% and at a 5% significance level (one-sided test) a number of n = 90 evaluable patients (45 in each arm eltrombopag/placebo) was required. After applying a correction for a loss to follow-up rate of 5%, 94 patients, i.e., 47 in each arm (eltrombopag/placebo), were to be enrolled. The chi-square test was used to compare categorical variables and the Mann-Whitney U test (nonparametric) or student t-test (parametric) was used to compare continuous variables. The probability of survival was analyzed using the method of Kaplan and Meier and log rank test. Cumulative incidences were estimated by the multi-stage method by Aalen-Johansen and compared between treatment arms by cox regression. A logistic regression of binary outcomes provided results with respect to the relevant covariates (disease severity, age). A significance level of 5% was used for all explorative analyses.<br>An interim analysis was neither planned nor performed. |
| Substantial protocol changes | The study was conducted according to the Clinical Study Protocol (CSP) version 1.15 dated 08 Jan 2015 and the following amendments:<br>• Version 2.0 dated 08 May 2017: change of financial support and marketing authorization holder of Investigational Medicinal Product (IMP)<br>• Version 3.0 dated 31 May 2017: corrections of terms and clarifications approved by the ethics committee<br>• Version 4.0 dated 03 Mar 2020: reduction of sample size and follow-up period, modification of the pharmacokinetic section, adjustment of eltrombopag treatment period<br>• Version 4.1 dated 22 Jul 2021: initial protocol for France<br>• Version 5.0 dated 28 Apr 2022: extension of recruitment period and adjustment of study timelines, addition of telomeric analysis and flow cytometry for Group A2 visit XIII<br>• Version 6.0 dated 09 Oct 2024: administrative changes at the Sponsor, addition of an exploratory endpoint, change of the end of trial definition |
| Publications | None by the time of finalization of this Clinical Study Report (CSR) |
| Financing | The study was financially supported by GlaxoSmithKline and Novartis. |

# Summary and conclusions

## Study subjects

Clinical conduct of the study was between 27 May 2015 (date of first informed consent) and 23 Dec 2024 (LPLV).

Ninety-three (93) patients were enrolled and screened at nine study centers. Of them, 85 patients successfully completed screening and were randomized to one of the two treatment arms, 44 of them to receive CSA plus placebo and 41 patients to receive CSA plus eltrombopag. Six months after therapy start, treatment was unblinded and patients newly assigned to treatment with CSA plus eltrombopag on the basis of their response assessment.

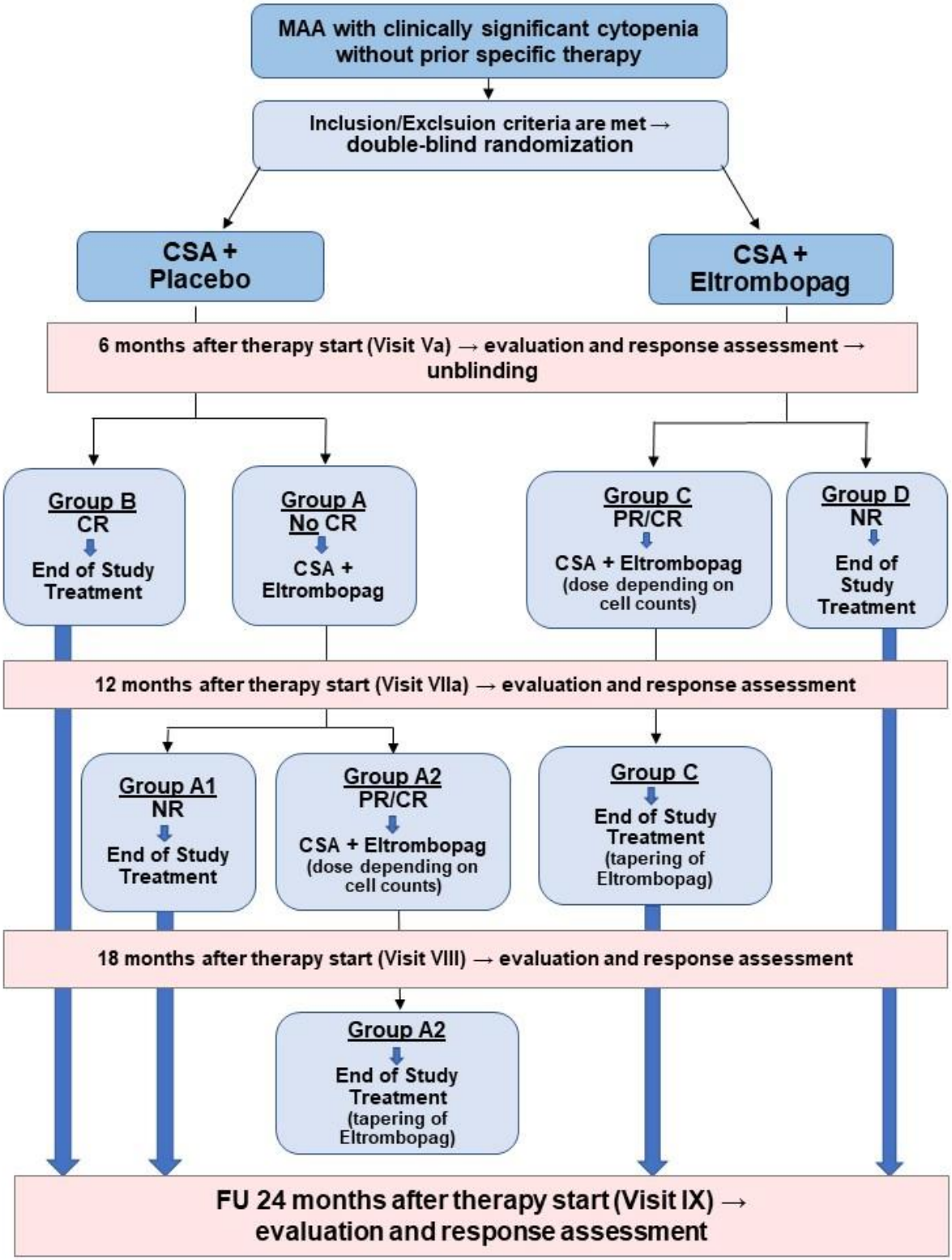
A further decision on treatment with CSA and eltrombopag was based on the 12-month response assessment. For group allocation and treatment see Figure 1.

The median age of patients was 53 years (range 19-84 years) with 37.6% of them being older than 60 years. 47.1% were female and 57.6% required transfusions within 12 weeks prior to enrollment. The median (Interquartile range, IQR) baseline platelet, neutrophil and hemoglobin concentrations were 22x10⁹/L (14-29x10⁹/L), 0.98x10⁹/L (0.64-1.29x10⁹/L), and 9.0 g/dL (8.2-9.8 g/dL), respectively. Patient characteristics in the two arms were well balanced. Ten patients discontinued before the 24-week evaluation (4 in the Placebo Arm and 6 in the Eltrombopag Arm) due to progression (3 in the Placebo Arm and 1 in the Eltrombopag Arm), adverse event (AE) (1 in the Eltrombopag Arm), withdrawal of informed consent (1 in the Eltrombopag Arm), and other reasons (4 patients).

One patient was wrongly allocated to Group C after response assessment at 6 months without having achieved trilineage response instead of correct assignment to Group D. Another patient was wrongly allocated to Group A1 after response assessment at 12 months although PR was achieved, instead of correct assignment to Group A2. Both patients were included in the analysis sets with the group to which they were assigned. However, this had no impact on the outcome of the primary endpoint, as the misclassification followed the response assessments at 6 and 12 months, respectively.

All 85 patients who received at least one dose of study medication were included in the FAS. Seventy-seven patients received treatment for ≥ 10 weeks and were included in the SAF, 41 in the Placebo Arm and 36 in the Eltrombopag Arm. For one of the SAF patients in each treatment arm no response assessment was available at visit Va. Therefore, these patients were excluded from the PPS.

**Figure 1: Trial flowchart**



## Evaluation of efficacy endpoints

### *Treatment exposure*

For 76/85 patients of the FAS (89.4%) treatment compliance was demonstrated, for 90.2% of patients in the Eltrombopag Arm and for 88.6% in the Placebo Arm.

Within the first 6 months of treatment, none of the patients in the Eltrombopag Arm required an interruption of eltrombopag while for 5 patients (12.2%) the eltrombopag dose was reduced due to increase in transaminases, CR, dose adjustment per protocol, platelets and elevated thromboembolic event risk at start of eltrombopag therapy. In 4 patients (9.8%) eltrombopag treatment was permanently stopped (2 patients end of study [EOS], 1 patient with progressive disease [PD] and 1 patient due to development of exanthema). For 5 patients of the Eltrombopag Arm (12.2%), an increase in dose was reported.

### *Primary endpoint*

The primary endpoint of the study was the trilineage hematologic response rate (CR + PR) at 6 months after start of study medication. The analysis of the primary endpoint was based on the PPS.

According to the investigator assessment 25/35 patients (71.4%, 95% confidence interval (CI) 54.8%-83.3%) showed trilineage hematologic response at 6 months after start of treatment with eltrombopag and 17/40 patients (42.5%; 95% CI 28.5%-57.8%) had hematologic response in the Placebo Arm. The response rate was significantly higher after treatment with eltrombopag as compared to the Placebo Arm (p=0.011; Fisher´s exact test; Odds ratio (OR) 3.325; lower limit (LL) for OR 1.354). Older age (above 60 years) did not have a significant impact on the outcome of the primary endpoint, whereas patients with transfusion-dependent MAA had a significantly lower chance of reaching the primary endpoint (p=0.007; OR 0.18; 95% CI [0.05; 0.63]).

### *Secondary endpoints*

### *Trilineage hematological response rate (CR and PR) at 3, 12 and 18 months*

At 3 months after treatment start, in the FAS 48.8% (20/41; 95% CI 34.3%-63.5%) of patients showed trilineage hematologic response in the Eltrombopag Arm and 25.0% (11/44; 95% CI 14.4% - 39.6%) in the Placebo Arm. The response rate was significantly higher after treatment with eltrombopag as compared to the Placebo Arm (p=0.020; OR 2.821; 95% confidence limit for OR 1.202).

After response assessment after 6 months and unblinding, patients in the Placebo Arm without CR (Group A) (n=38; 23 NR,15 PR) received eltrombopag in addition to continued CSA starting in month 6. This group achieved an ORR of 73.5% at 6 months (25/34 patients with an available 6-month assessment: 9 NR, 14 PR, 11 CR; 4 not assessed; p=0.009, McNemar test, comparing ORR at 6 months vs. 12 months in Group A, i.e., before vs. after adding eltrombopag. Thus, adding eltrombopag to Placebo Arm patients without CR after 6 months increased both the ORR rate and the strength of response. Despite this improvement by addition of eltrombopag in Group A at 6 months, the cumulative incidence of trilineage response was superior in patients who had been initially randomized to eltrombopag (HR 1.71; p=0.039).

After 12 months, significant differences were seen between the following groups: A versus C (p=0.046, OR 0.256, 95% CI [0.042; 1.100]), A versus D (p=0.026, OR 6.448, 95% CI [1.032; 72.473]) and C versus D (p=0.001, OR 22.938, 95% CI [2.832; 329.315]). After 18 months, most significant differences were seen between the following groups: A2 versus D (p=0.019, OR 12.265, 95% CI [1.345; 610.074]) and C versus D (p=0.007, OR 13.969, 95% CI [1.492; 705.743]).

### *Single lineage response*

Neutrophil response was significantly improved after 3 months of eltrombopag treatment as compared to the Placebo Arm (p=0.012; OR 2.984; 95% LL for OR 1.308). However, after 6 months, the difference between the treatment arms was no longer statistically significant different. The erythroid response showed no significant difference between the treatment arms, neither after 3 nor after 6 months. The platelet response was significantly improved after 6 months of eltrombopag treatment as compared to the Placebo Arm (p=0.034; OR 2.443; 95% LL for OR 1.081), but not yet after 3 months.

### *Cumulative incidence of trilineage response*

Cumulative incidence of trilineage response at 6 months in the Eltrombopag Arm was higher than in the Placebo Arm. After response assessment and unblinding, patients in the Placebo Arm who had not achieved CR by month 6, could have received eltrombopag in addition to ongoing CSA (Group A, n=38). Four patients assigned to Group A did not receive eltrombopag. Twenty-five patients of Group A achieved PR (n=14) or CR (n=11) by the evaluation at 12 months, i.e. 6 months of eltrombopag treatment. Thus, by month 12, the trilineage hematological response showed almost the same cumulative incidence in both treatment arms, because the additional administration of eltrombopag from month 6 onwards in patients in the Placebo Arm without CR after 6 months led to an almost identical cumulative response rate as in patients who were initially randomized to the Eltrombopag Arm. The subgroup analysis showed evidence for a lower incidence of trilineage response in patients older than 60 years with transfusion-dependent MAA (HR 0.41; p=0.016).

### *Time to best hematological and single lineage response*

The median time to best trilineage response for patients with response in the FAS population was 8.31 months, with 6.95 months in the Eltrombopag and 9.20 months in the Placebo Arm. The median time to reach single lineage response was 7.08 months (erythroid), 5.52 months (platelet) and 2.91 months (neutrophil). A significant difference between the Placebo and Eltrombopag Arm was observed only for neutrophil response (p=0.025).

### *Proportion of patients with need for transfusions and number of units transfused*

There was no significant difference between the treatment arms in the proportion of patients requiring transfusions and in the number of transfused units. In the FAS population, a median number of 6 units of PC and 7 units of pRBC were transfused within the first 6 months.

### *Cumulative incidence of progression to SAA/VSAA or intensive immunosuppressive treatment with ATG*

Two cases of progression were reported in the Eltrombopag Arm after evaluation of the primary endpoint whereas no such case was observed in the Placebo Arm.

### *Toxicity profile as measured using the CTCAE criteria*

No treatment-emergent adverse events (TEAEs) of Grade 4 or 5 were observed within the first 6 months after therapy start. The following TEAEs of Grade 3 occurring during the first 10 weeks of treatment were assessed as related to the study medication (eltrombopag or placebo): hypertension (1 patient each in the Eltrombopag and Placebo Arm), decreased platelet count (1 patient in the Placebo Arm) and paresthesia (1 patient in the Placebo Arm). TEAEs of Grade 3 reported between 10 weeks and 6 months and assessed as related to the study medication were hypertension (1 patient in the Placebo Arm) and decreased platelet count (1 patient in the Eltrombopag Arm). No TEAEs of Grade 5 were reported beyond 6 months after treatment initiation. A total of 15 patients (19.5%) experienced Grade 3 and 4 TEAEs of which stomatitis (1 patient), maculo-papular rash (1 patient) and thrombosis (1 patient) were assessed as related to study treatment.

### *Relapse rate at 6, 12 and 18 months*

Comparison of treatment arms revealed a significant difference with respect to the relapse rate at 6 months (p=0.024).

### *Cumulative incidence of relapse (from best hematological response)*

The proportion of responders with relapse tended to be higher in the Eltrombopag Arm. However, comparison of treatment arms and subgroup analysis did not show a statistically significant difference. In relation to the duration of eltrombopag therapy, the number of recurrences after 6 months of eltrombopag therapy was approximately the same (5 versus 4 patients).

#### *Cumulative incidence of relapse (from best hematological response, modified criteria)*

This relapse definition was very broad and included also minor, clinically not significant declines of blood counts when still response criteria were fulfilled. Therefore, additionally a post-hoc analysis with modified relapse criteria was performed. Relapse from first trilineage response was defined as no longer meeting criteria for at least PR (i.e., patients must have received at least PR – and the next assessment which did no longer fulfill criteria for at least PR was considered as relapse (modified criteria). This is a common relapse definition in AA trials and allows better comparison to results of other trials. This analysis did not show a significant difference in relapse rate by treatment arm.

### *Overall survival (OS)*

Three cases of death were reported, all occurred in the Eltrombopag Arm. Median OS could not be calculated.

### *Failure free survival (FFS)*

No significant difference was found between treatment arms (p=0.872). The median FFS was 24.86 weeks (95% CI 24.00; 87.29) in the Eltrombopag Arm and 24.29 weeks (95% CI 24.00; 36.00) in the Placebo Arm. Applying modified relapse criteria, the median FFS was 49.00 weeks (95% CI 24.43; NA) in the Eltrombopag Arm and 24.29 weeks (95% CI 24.00; 41.71) in the Placebo Arm. The difference did also not reach statistical significance (p=0.187).

Pairwise comparison revealed a significant difference in groups A versus D (p=0.015), B versus D (p=0.009) and C versus D (p=0.001). The median FFS was longest in Group C with

99.00 weeks.

### *Telomere lengths and presence of telomerase mutations as biomarkers for response*

Subgroup analysis showed no evidence that telomere length was associated with probability of trilineage hematologic response.

### *Quality of life (QoL)*

Overall, 75/85 patients in the FAS population (88.2%) completed the QLQ-C30 questionnaire at therapy start and 73/85 patients (85.9%) after 6 months of treatment.

After 24 weeks of treatment, the global health status had improved in 23.5% of patients and the QoL summary score in 15.3% of patients. Among the different scales, cognitive functioning had improved in 32.9% of patients with a significant higher rate of improvement in the Eltrombopag Arm (48.8% versus 18.2%). Role functioning, social functioning and fatigue had improved in the majority of patients independent of the treatment. In the other scales, the majority of patients reported no change. A total of 18.8% of patients reported improvement of financial difficulties with a significant higher rate in the Eltrombopag Arm (31.7% versus 6.8%).

The mean FACIT-F score for all patients of the FAS population was 19.6 at therapy start and decreased during treatment with eltrombopag or placebo by 1.3 as compared to the baseline with no obvious difference between the treatment arms.

With regard to QLQ-AA/PNH, among the different scales, infections had improved in 27.1% of patients with a significant higher rate of improvement in the Eltrombopag Arm (41.5% versus A13.6%). However, for all scales, the majority of patients reported no change from baseline to 24 weeks after treatment start.

## Evaluation of safety endpoints

No serious adverse drug reactions (SADRs) occurred within the first 6 months of treatment. Eltrombopag was well tolerated. There were no differences in ADRs between placebo and eltrombopag. In the context of potential side effects of eltrombopag and the background medication with CSA, it should be noted that no bleeding after discontinuation of eltrombopag therapy, and no bone marrow fibrosis were observed in this study. There was one case of newly diagnosed cataracts in the Eltrombopag Arm within the first 6 months. With regard to CSA, it should be noted that there were some patients with an increase in creatinine levels, but the frequency and the grade of creatinine increase was not unusual for AA patients receiving CSA treatment.

Only three serious adverse events (SAEs) occurred that were assessed as related to the study medication. One patient suffered from thrombosis, one developed pulmonary embolism and another presented with pyrexia. These SAEs were expected according to the reference safety information. Thus, no additional risks or new toxicities for eltrombopag treatment in the dosing regimen applied in this study with concomitant CSA background medication had emerged during the course of the study.

There were no TEAEs with fatal outcome. Three cases of death were reported. Two patients died within the follow-up period (after 53.7 weeks and 72.1 weeks). Since this was outside the reporting period for AEs, no information on the cause of death was available. Another patient died from uremia and kidney failure after 6.7 weeks. Treatment with study medication had been

stopped before due to decreased absolute neutrophil count (ANC).

Only a small proportion of patients (maximum 7 patients; 9.25% per parameter) showed clinically significant laboratory abnormalities. The parameters affected and the extent of the change were within the range expected for the underlying disease, with accompanying PNH clones and treatment with transfusions and CSA. The most common finding, and one that became increasingly prevalent over time, was elevated creatinine levels, which is a known adverse effect of treatment with CSA. Elevated ferritin can be explained by the underlying disease in combination with transfusion-related iron intake.

No change of weight during the treatment period was noted. There was a tendency for slight increase of both systolic and diastolic blood pressure. This was observed in both arms and was most likely due to background treatment with CSA. There was no obvious difference in systolic or diastolic blood pressure between the treatment arms. If any, the differences were minimal, and the median systolic and diastolic pressure was higher in the Placebo Arm at most observation times.

There were no signals of differences in the number or type of abnormal electrocardiogram (ECG) findings among the Eltrombopag or Placebo Arms and no increase of abnormal findings comparing the first 6 months and after 6 months.

Regarding ophthalmologic examination, there were some differences in the baseline investigation, e.g. more patients with glasses / contact lenses or more lenticular changes in the Eltrombopag Arm. In further follow-up examinations, only a few patients had findings that were not already present at baseline. In the first 6 months, 6 and 4 new findings were detected in the Eltrombopag and the Placebo Arm, respectively.

Abnormal findings in cytogenetics at baseline were in the expected range of newly diagnosed patients. In follow-up examinations, there was no evidence for marked clonal evolution. The type of abnormal findings (e.g. trisomy 8, monosomy 7, mutation in PIGA or DNMTA3A) are quite common in aplastic anemia (AA), also without eltrombopag treatment. Thus, this data did not provide a signal that eltrombopag might promote clonal evolution.

For an overall summary of patients with TEAEs during the different study periods see Table 1 to Table 3. The number of patients with TEAEs and adverse drug reactions (ADRs) by System Organ Class (SOC) and SAEs by SOC and Preferred Term (PT) is summarized in Table 4 to Table 9.

**Table 1: Overall summary of number of patients with TEAEs reported within the first 10 weeks after therapy start (SAF)**

| Number of patients with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| AE (serious or not, related or not) | 31 | 86.1 | 39 | 95.1 | 70 | 90.9 |
| ADR (serious or not) | 14 | 38.9 | 15 | 36.6 | 29 | 37.7 |
| SAE (related or not) | 3 | 8.3 | 5 | 12.2 | 8 | 10.4 |

**Table 2: Overall summary of number of patients with TEAEs reported between 10 weeks and 6 months after therapy start (SAF)**

| Number of patients with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| AE (serious or not, related or not) | 30 | 83.3 | 28 | 68.3 | 58 | 75.3 |
| ADR (serious or not) | 10 | 27.8 | 6 | 14.6 | 16 | 20.8 |
| SAE (related or not) | 4 | 11.1 | 4 | 9.8 | 8 | 10.4 |

**Table 3: Overall summary of number of patients with TEAEs reported later than 6 months after therapy start (SAF)**

| Number of patients with at least one such event | A1 N=5 | | A2 N=29 | | B N=2 | | C N=26 | | D N=9 | | Other N=14 | | Total N=77 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| AE | 5 | 100.0 | 28 | 96.6 | 1 | 50.0 | 20 | 76.9 | 2 | 22.2 | 2 | 14.3 | 58 | 75.3 |
| ADR | 3 | 60.0 | 9 | 31.0 | 0 | 0.0 | 6 | 23.1 | 0 | 0.0 | 0 | 0.0 | 18 | 23.4 |
| SAE | 1 | 20.0 | 9 | 31.0 | 0 | 0.0 | 5 | 19.2 | 0 | 0.0 | 2 | 14.3 | 17 | 22.1 |
| SADR | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 2 | 7.7 | 0 | 0.0 | 0 | 0.0 | 2 | 2.6 |

**Table 4: Number of patients with TEAEs reported within the first 10 weeks after therapy start by SOC (SAF)**

| Number of patients with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Total | 31 | 86.1 | 39 | 95.1 | 70 | 90.9 |
| Gastrointestinal disorders | 19 | 52.8 | 25 | 61.0 | 44 | 57.1 |
| Nervous system disorders | 19 | 52.8 | 24 | 58.5 | 43 | 55.8 |
| General disorders and administration site conditions | 13 | 36.1 | 20 | 48.8 | 33 | 42.9 |
| Musculoskeletal and connective tissue disorders | 12 | 33.3 | 19 | 46.3 | 31 | 40.3 |
| Respiratory, thoracic and mediastinal disorders | 11 | 30.6 | 13 | 31.7 | 24 | 31.2 |
| Infections and infestations | 9 | 25.0 | 13 | 31.7 | 22 | 28.6 |
| Skin and subcutaneous tissue disorders | 8 | 22.2 | 10 | 24.4 | 18 | 23.4 |
| Vascular disorders | 8 | 22.2 | 9 | 22.0 | 17 | 22.1 |
| Investigations | 5 | 13.9 | 6 | 14.6 | 11 | 14.3 |
| Hepatobiliary disorders | 9 | 25.0 | 1 | 2.4 | 10 | 13.0 |
| Renal and urinary disorders | 4 | 11.1 | 5 | 12.2 | 9 | 11.7 |
| Ear and labyrinth disorders | 4 | 11.1 | 4 | 9.8 | 8 | 10.4 |
| Metabolism and nutrition disorders | 3 | 8.3 | 5 | 12.2 | 8 | 10.4 |
| Eye disorders | 5 | 13.9 | 1 | 2.4 | 6 | 7.8 |

| Number of patients with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Psychiatric disorders | 2 | 5.6 | 4 | 9.8 | 6 | 7.8 |
| Cardiac disorders | 2 | 5.6 | 2 | 4.9 | 4 | 5.2 |
| Reproductive system and breast disorders | 2 | 5.6 | 2 | 4.9 | 4 | 5.2 |
| Blood and lymphatic system disorders | 1 | 2.8 | 1 | 2.4 | 2 | 2.6 |
| Injury, poisoning and procedural complications | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Surgical and medical procedures | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |

**Table 5: Number of patients with ADRs reported within the first 10 weeks after therapy start by SOC (SAF)**

| Number of subjects with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Total | 14 | 38.9 | 15 | 36.6 | 29 | 37.7 |
| Nervous system disorders | 5 | 13.9 | 10 | 24.4 | 15 | 19.5 |
| General disorders and administration site conditions | 3 | 8.3 | 8 | 19.5 | 11 | 14.3 |
| Gastrointestinal disorders | 6 | 16.7 | 4 | 9.8 | 10 | 13.0 |
| Investigations | 3 | 8.3 | 3 | 7.3 | 6 | 7.8 |
| Musculoskeletal and connective tissue disorders | 2 | 5.6 | 2 | 4.9 | 4 | 5.2 |
| Skin and subcutaneous tissue disorders | 1 | 2.8 | 3 | 7.3 | 4 | 5.2 |
| Vascular disorders | 1 | 2.8 | 3 | 7.3 | 4 | 5.2 |
| Renal and urinary disorders | 2 | 5.6 | 1 | 2.4 | 3 | 3.9 |
| Infections and infestations | 2 | 5.6 | 0 | 0.0 | 2 | 2.6 |
| Metabolism and nutrition disorders | 2 | 5.6 | 0 | 0.0 | 2 | 2.6 |
| Blood and lymphatic system disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Psychiatric disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |

**Table 6: Number of patients with SAEs reported within the first 10 weeks after therapy start by SOC and PT (SAF)**

| Number of subjects with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Total | 3 | 8.3 | 5 | 12.2 | 8 | 10.4 |
| Infections and infestations | 0 | 0.0 | 3 | 7.3 | 3 | 3.9 |
| Appendicitis | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Meningitis | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Pneumonia | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| General disorders and administration site conditions | 1 | 2.8 | 1 | 2.4 | 2 | 2.6 |
| Pyrexia | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Fatigue | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Blood and lymphatic system disorders | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Anemia | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Eye disorders | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Visual impairment | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Gastrointestinal disorders | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Abdominal pain | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Metabolism and nutrition disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Hyperkalemia | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Nervous system disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Syncope | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Surgical and medical procedures | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Tooth extraction | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |

**Table 7: Number of patients with TEAEs reported between 10 weeks and 6 months after therapy start by SOC (SAF)**

| Number of subjects with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Total | 30 | 83.3 | 28 | 68.3 | 58 | 75.3 |
| Gastrointestinal disorders | 11 | 30.6 | 16 | 39.0 | 27 | 35.1 |
| Skin and subcutaneous tissue disorders | 10 | 27.8 | 14 | 34.1 | 24 | 31.2 |
| Nervous system disorders | 10 | 27.8 | 8 | 19.5 | 18 | 23.4 |
| Infections and infestations | 10 | 27.8 | 6 | 14.6 | 16 | 20.8 |
| Investigations | 5 | 13.9 | 3 | 7.3 | 8 | 10.4 |
| Vascular disorders | 3 | 8.3 | 4 | 9.8 | 7 | 9.1 |
| General disorders and administration site conditions | 4 | 11.1 | 2 | 4.9 | 6 | 7.8 |
| Musculoskeletal and connective tissue disorders | 4 | 11.1 | 2 | 4.9 | 6 | 7.8 |
| Respiratory, thoracic and mediastinal disorders | 4 | 11.1 | 2 | 4.9 | 6 | 7.8 |
| Cardiac disorders | 2 | 5.6 | 2 | 4.9 | 4 | 5.2 |
| Metabolism and nutrition disorders | 2 | 5.6 | 2 | 4.9 | 4 | 5.2 |
| Hepatobiliary disorders | 2 | 5.6 | 1 | 2.4 | 3 | 3.9 |
| Renal and urinary disorders | 1 | 2.8 | 2 | 4.9 | 3 | 3.9 |
| Reproductive system and breast disorders | 1 | 2.8 | 2 | 4.9 | 3 | 3.9 |
| Blood and lymphatic system disorders | 1 | 2.8 | 1 | 2.4 | 2 | 2.6 |
| Ear and labyrinth disorders | 0 | 0.0 | 2 | 4.9 | 2 | 2.6 |
| Surgical and medical procedures | 0 | 0.0 | 2 | 4.9 | 2 | 2.6 |
| Eye disorders | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Immune system disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Injury, poisoning and procedural complications | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Psychiatric disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |

**Table 8: Number of patients with ADRs reported between 10 weeks and 6 months after therapy start by SOC (SAF)**

| Number of subjects with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Total | 10 | 27.8 | 6 | 14.6 | 16 | 20.8 |
| Skin and subcutaneous tissue disorders | 4 | 11.1 | 3 | 7.3 | 7 | 9.1 |
| Gastrointestinal disorders | 4 | 11.1 | 1 | 2.4 | 5 | 6.5 |
| Investigations | 3 | 8.3 | 1 | 2.4 | 4 | 5.2 |
| Nervous system disorders | 1 | 2.8 | 3 | 7.3 | 4 | 5.2 |
| Vascular disorders | 2 | 5.6 | 1 | 2.4 | 3 | 3.9 |
| Renal and urinary disorders | 0 | 0.0 | 2 | 4.9 | 2 | 2.6 |
| Ear and labyrinth disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Respiratory, thoracic and mediastinal disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |

**Table 9: Number of patients with SAEs reported between 10 weeks and 6 months after therapy start by SOC (SAF)**

| Number of subjects with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Total | 4 | 11.1 | 4 | 9.8 | 8 | 10.4 |
| Investigations | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Blood bilirubin increased | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Nervous system disorders | 0 | 0.0 | 2 | 4.9 | 2 | 2.6 |
| Cerebral venous thrombosis | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Syncope | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Blood and lymphatic system disorders | 1 | 2.8 | 1 | 2.4 | 2 | 2.6 |
| Hemolysis | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Anemia | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Cardiac disorders | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Myocardial infarction | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| General disorders and administration site conditions | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Condition aggravated | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Infections and infestations | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| COVID-19 pneumonia | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Injury, poisoning and procedural complications | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Subcutaneous hematoma | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |

## Conclusions

Adding eltrombopag to CSA treatment for patients with untreated MAA significantly improved trilineage hematologic response by Week 24. The addition of eltrombopag in patients with MAA without CR after 24 weeks of single-agent CSA treatment also improved the trilineage hematologic response rate. Treatment with eltrombopag was well tolerated, and no new safety concerns were identified in patients with MAA. Eltrombopag combined with standard CSA therapy shows a clear advantage in initial treatment for patients with MAA and could become the new standard of care for MAA patients, administered orally on an outpatient basis.

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# 4 List of abbreviations and definition of terms

| | |
|---|---|
| AA | Aplastic anemia |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| AML | Acute myeloid leukemia |
| ANC | Absolute neutrophil count |
| AP | Alkaline phosphatase |
| AST | Aspartate aminotransferase |
| ATG | Antithymocyte globulin |
| ATGAM® | equine ATG, Pfizer |
| AUC | Area under the curve |
| BMFS | Bone marrow failure syndrome |
| BUN | Blood urea nitrogen |
| CBC | Complete blood count |
| CI | Confidence interval |
| c-MPL | Thrombopoietin receptor |
| CPI | Coordinating Principal Investigator |
| CR | Complete response |
| CRF | Case report form |
| CRO | Clinical Research Organization |
| CSA | Ciclosporin A |
| CSP | Clinical study protocol |
| CSR | Clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DBL | Database lock |
| DSMB | Data safety monitoring board |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EMA | European Medicines Agency |
| EMAA | Eltrombopag in combination with Ciclosporin in Patients with Acquired Moderate Aplastic Anemia |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EOS | End of study |
| FAS | Full analysis set |
| FDA | Food and Drug Administration |
| FFS | Failure-free survival |
| FPFV | First patient first visit |
| FU | Follow-up |
| GCP | Good Clinical Practice |
| GGT | Gamma-glutamyl transferase |
| GMP | Good Manufacturing Practice |
| GPI-AP | Glycosylphosphatidylinositol-anchored proteins |
| G-CSF | Granulocyte colony stimulating factor |
| hATG | Equine ATG |
| HgB | Hemoglobin |
| HIV | Human immunodeficiency virus |
| IB | Investigator's Brochure |
| ICF | Informed consent form |
| IEC | Independent ethics committee |
| ICH | International Council for Harmonization |
| ID | Identification |
| IMP | Investigational medicinal product |

| | |
|---|---|
| INR | International normalized ratio |
| IQR | Interquartile range, displayed as Q25-Q75 |
| IRB | Institutional Review Board |
| ISF | Investigator Site File |
| ITP | Idiopathic thrombocytopenic purpura |
| LDH | Lactate dehydrogenase |
| LL | Lower limit |
| LPFV | Last patient first visit |
| LPLV | Last patient last visit |
| MAA | Moderate aplastic anemia |
| MDS | Myelodysplastic syndrome |
| MMF | Mycophenolate mofetil |
| NA | Not applicable |
| NR | No response |
| OR | Odds ratio |
| OS | Overall survival |
| Pat-ID | Patient identification number (subject number) |
| PC | Platelet concentrate |
| PD | Progressive disease |
| PI | Principal Investigator |
| PK | Pharmacokinetics |
| PML | Progressive multifocal leukoencephalopathy |
| PNH | Paroxysmal nocturnal hemoglobinuria |
| PPS | Per-protocol set |
| PR | Partial response |
| PRBC | Packed red blood cells |
| PT | Preferred term |
| Pts | Patients |
| PTT | Partial thromboplastin time |
| PVAN | Polyoma virus-associated nephropathy |
| QLQ | Quality of life questionnaire |
| QoL | Quality of life |
| SAA | Severe aplastic anemia |
| SADR | Serious adverse drug reaction |
| SAE | Serious adverse event |
| SAF | Safety analysis set |
| SAP | Statistical analysis plan |
| STD | Standard deviation |
| SmPC | Summary of Product Characteristics |
| SOC | System organ class |
| STL | Shortened telomere length |
| SUSAR | Suspected unexpected serious adverse reaction |
| TEAE | Treatment-emergent adverse event |
| TL | Telomere length |
| TMF | Trial Master File |
| TPO | Thrombopoietin |
| TPO-R | Thrombopoietin-receptor |
| ULN | Upper limit of normal |
| US | United States of America |
| V | Visit |
| VSAA | Very severe aplastic anemia |
| WBC | White blood cell count |
| WHO | World Health Organization |

# 5 Ethics

## 5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The clinical study protocol (CSP) and any amendments as well as the informed consent form (ICF), Investigator's Brochure of eltrombopag (IB) and any other relevant documents were reviewed and approved by each study site's IEC before the start of the study. A list of all IECs consulted can be found in Appendix 16.1.3.

## 5.2 Ethical conduct of the study

Performance, evaluation, and documentation of this study were specified in the CSP to ensure that the sponsor and investigator abide to the International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, the principles set out in the Declaration of Helsinki and applicable local law(s) and regulation(s). Strict adherence to all specifications described in the CSP was required, i.e., the investigator was not allowed to modify or change the procedures described in the CSP. Deviations from the protocol were to be documented and explained by the investigator and/or sponsor.

Documented approval from the competent IEC was obtained for the participating centers before start of the study. All investigators and other staff involved in the study were informed that the competent federal authorities and authorized representatives of the sponsor have the right to review study documentation and the study subjects' medical records at any time.

## 5.3 Patient information and consent

The patient information sheet, ICF, all other documents handed out to the trial subject and any recruitment advertisements (if applicable) were reviewed and approved by the IEC before their use. All written information handed out to the trial subjects were revised whenever new information relevant to the subject´s consent became available.

Trial subjects were not enrolled into the study unless they had voluntarily consented to take part in the trial, after having been informed verbally and in writing in comprehensible language of the nature, scope and possible consequences of the study by the investigator. The subjects also agreed that representatives of the sponsor (e.g., monitors or auditors) or the competent supervisory or federal authorities might be given access to the data recorded within the framework of the clinical trial. The trial subject was informed of the potential benefits and possible side effects of the investigational medicinal product (IMP) applied in this study.

Before entering the study, the ICF was read by and explained to all subjects. Each subject had ample time and opportunity to ask questions and was informed about the right to withdraw his/her consent at any time without giving reasons and without jeopardizing his/her further medical care.

The ICF was signed by the trial subjects and also signed and dated by the investigator. The originally signed ICF is archived in the investigator site file (ISF). Each subject received a copy of the written information sheet, confirmation of insurance inclusive conditions, and the signed ICF.

A copy of a representative patient information sheet and informed consent form is provided in Appendix 16.1.3.

# 6 Investigators and study administrative structure

The study was performed under the organization of the University Hospital of Ulm, University of Ulm, Medical Faculty which acted as sponsor.

Dr. Britta Höchsmann (Institute of Transfusion Medicine, University of Ulm) was appointed as *Leiter der klinischen Prüfung* (Coordinating Principal Investigator) according to German Drug Law. Dr. Britta Höchsmann was also responsible for medical coordination including medical advises and publications.

Only qualified investigators were selected to take part in the study and investigate the study drug. At each center, the principal investigator was responsible for the study. A list of participating centers and investigators is given in Section 2 Synopsis. The signature of the Coordinating Investigator and the sponsor representative on page 2 of this clinical study report (CSR) indicates that the report accurately describes the conduct and results of this study.

Key study personnel involved in the conduct of this study is listed in Table 10.

Local laboratories performed safety measurements, blood chemistry, full blood count with differential reticulocyte count, microscopic peripheral blood count and cytogenetic analysis according to local standard procedures. A central morphology review (if necessary), GPI-AP flow cytometry and translational research were conducted in the central lab Ulm. Telomere analysis was conducted in the central lab Aachen.

Statistical analyses were performed by GWT-TUD GmbH according to an approved SAP and to the CSP.

An independent data safety monitoring board (DSMB) was formed to oversee the safety of the trial subjects in the clinical study by periodically assessing the safety of the trial therapy (see Table 10).

**Table 10: Study administrative structure**

| Responsibility | Name | Affiliation/Address |
|---|---|---|
| Sponsor | University Hospital of Ulm | University of Ulm, Medical Faculty<br>Albert-Einstein-Allee 29<br>89081 Ulm, Germany |
| Coordinating Investigator | Dr. Britta Höchsmann | Institute of Transfusion Medicine,<br>University of Ulm<br>Helmholtzstrasse 10<br>89081 Ulm, Germany |
| Project management<br>Data management<br>Safety management<br>Monitoring | In function of CRO | GWT TUD GmbH<br>Freiberger Strasse 33<br>01067 Dresden, Germany |
| Statistical analyses | Dr. Dorothea Schipp<br>on behalf of the CRO | GWT TUD GmbH<br>Freiberger Strasse 33<br>01067 Dresden, Germany |
| Central laboratory | Telomere diagnostics | Hämatologisches Labor/Telomerdiagnostik<br>Klinik für Hämatologie, Onkologie, Hämostaseologie und SZT<br>Pauwelsstrasse 30<br>52074 Aachen, Germany |
| | Flow cytometric diagnostics | University of Ulm<br>Helmholtzstrasse 10<br>89081 Ulm, Germany |
| DSMB | Prof. Dr. Jörg Schubert | Elblandklinikum Riesa<br>Klinik für Innere Medizin<br>Hämatologie, Onkologie und Palliativmedizin<br>Weinbergstrasse 8<br>01589 Riesa, Germany |
| | Prof. Dr. Paul Graf La Rosée | Schwarzwald-Baar Klinikum Villingen-Schwenningen GmbH<br>Klinik für Innere Medizin II: Onkologie, Hämatologie, Immunologie, Infektiologie und Palliativmedizin<br>Klinikstrasse 11<br>78052 Villingen-Schwenningen, Germany |
| | Prof. Dr. Norbert Frickhofen | Humperdinckstrasse 28<br>65193 Wiesbaden, Germany |
| | PD Dr. Michael Lauseker | Institut für Medizinische Informationsverarbeitung, Biometrie und Epidemiologie (IBE)<br>Marchioninistrasse 15<br>81377 München, Germany |

# 7 Introduction

## 7.1 Background information

Moderate aplastic anemia (MAA) is a non-malignant hematological disease. It is characterized by a bone marrow failure leading to cytopenia with the possibility of relevant symptoms such as anemia, infections and bleedings as well as reduced quality of life (QoL) [2].

Outcome of aplastic anemia (AA) has been improved substantially over the last three decades due to the establishment of the main treatment approaches stem cell transplantation and immunosuppressive therapy with ciclosporin A (CSA) and antithymocyte globulin (ATG) into standard therapy.

Specific treatment is required if patients are transfusion-dependent or if the patient is at risk (infections, bleeding) due to cytopenia. MAA is not an indication for allogeneic stem cell transplantation. In case of indication for a specific therapy, standard first line treatment is immunosuppression [1]. CSA is an immunosuppressant which reduces the activity of the immune system by interfering with the activity and proliferation of T-cells. CSA is highly active in the therapy of AA and has become an integral part of all immunosuppressive first-line regimens [3]-[10].

A prospective, randomized trial demonstrated higher response rate and better failure-free survival (FFS) with the combination treatment of horse antithymocyte globulin (hATG)+CSA as compared to hATG without CSA [11][12]. A follow-up 11 years after initial treatment confirmed the advantage of the combination of hATG+CSA regarding response rate and FFS [12]. Patients treated with hATG+CSA responded more quickly than patients treated with hATG without CSA (median time to response 60 days after hATG+CSA versus 82 days after hATG). [11][12]. The overall survival (OS) at 11.3 years did not differ between the hATG and the hATG+CSA group. However, most patients in the hATG+CSA group received only one course of treatment, whereas many patients in the hATG group required salvage treatments [12]. Thus, the addition of CSA to hATG significantly reduced early treatment failures and resulted in improved long-term FFS (39% vs. 24% after 11 years) [11][12].

Since the initial report several studies have confirmed the efficacy of the combination regimen of hATG+CSA with response rates of > 60% after 3-6 months and good long-term survival [13]-[20].

In a study of the EBMT WP AA on immunosuppression for MAA, 115 patients with MAA were randomized to receive CSA (n = 61) or hATG+CSA (n = 54) [1]. In the CSA group, the percentage of complete and partial responders was 23% and 23%, respectively, for an overall response rate of 46%. A significantly higher overall response rate of 74% was found in the hATG+CSA group, with 57% complete and 17% partial responders (p = 0.02). However, despite the different response rates the probability of OS for the two groups was comparable, 93% (CSA group) and 91% (hATG+CSA group) [1].

The clinical trial in MAA [1] as the pivotal trial on immunosuppression for severe and very severe aplastic anemia (SAA/VSAA) was conducted with hATG. The only available hATG preparation (Lymphoglobulin®) was withdrawn from the European market in 2007. Thus, by the time of the start of this study only rabbit ATG (rATG) was registered for treatment of AA in Europe. Recent trials demonstrated that response rate and OS in patients with SAA/VSAA was significantly lower after rATG as compared to hATG [21][22]. No data about the efficacy of

rATG in MAA were available by the start of the current study.

Since the withdrawal of the hATG Lymphoglobuline® from the European market, the only available hATG is ATGAM® which is registered in the US. ATGAM® is not licensed in Europe. Reimbursement for health insurances of this non-licensed product is a matter of debate [1][23][24].

Additionally, there are a number of patients who cannot (or only on a limited basis) be treated with intensified immunosuppressive therapies due to potential side effects and complications. It was shown that patients who fail to respond to CSA may later respond to ATG. Thus, sequential treatment starting with CSA monotherapy, which can be used in an outpatient setting and avoids the immediate and late side effects of ATG, and proceeding to ATG in non-responders is an option in patients with MAA.

It has also been noted that the duration of CSA treatment and individual titration of CSA dose has a significant influence on relapse rate and durability of response: In a subgroup of patients CSA-dependent responses are noted, i.e. discontinuation of CSA or lowering the CSA dose led to a decrease of blood counts [11][12][25][26]. In the German prospective trial, 26% of responders required CSA for more than 6 months and 14% of patients had CSA-dependent response [11][12]. There is no clear consensus on the protocol for taper of CSA. In a retrospective study in children, relapse risk was significantly associated with rapid discontinuation of CSA [25]. In contrast, a study in adults demonstrated that prolonged administration of CSA did not prevent relapses, but the time to relapse was prolonged by about one year with prolonged CSA administration [26]. Mycophenolate mofetil (MMF) was studied as adjunct to ATG+CSA treatment in an attempt to improve response rate and survival and reduce the relapse rate [27]. In this trial, CSA was stopped after 6 months and immunosuppression was continued only with MMF. The relapse rate was high (37% at a median of about 13 months) and over half of the relapses occurred during ongoing MMF treatment [27].

These observations on CSA-dependent responses and impact of CSA duration/dose on durability of response also support the efficacy of CSA in AA.

Because of its efficacy and the moderate side effects, CSA is the most commonly used drug in AA. Nevertheless, France is the only country participating in the EMAA-trial with an approval for CSA in the indication AA. In all other participating countries, the use of CSA is off-label but basically recommended in national and international guidelines [10][23][28]-[30].

Patients fulfilling the enrollment criteria of this trial also fulfill criteria for immunosuppressive treatment due to symptoms or risk of cytopenia. In this situation, the eligible patients would also receive treatment with CSA as current standard of care if they are not enrolled in this clinical trial regardless of randomization group. Therefore, CSA is included as a background therapy for all patients regardless of randomization group. In MAA patients requiring therapy (i.e., the target population of this trial) it cannot be justified to omit this baseline treatment with CSA and to study eltrombopag versus placebo alone without immunosuppression. Since this trial enrolled patients with new onset of treatment indication, the background therapy with CSA was started at the same time as the investigational drug eltrombopag or placebo. At the beginning of this trial, eltrombopag was traded by GlaxoSmithKline. The rights of trading of eltrombopag were later on passed to Novartis as well as the support for the EMAA trial.

In spite of the high efficacy of immunosuppression, a significant number of patients have

persistent cytopenias or do not respond at all [31]. Even after first-line treatment with ATG/CSA, 26% of patients did not respond [1]. Finally, there is a lack of efficient therapeutic options with tolerable toxicity profiles for this patient group (especially elderly patients). Therefore, the current treatment policy for this group of patients consists of regular transfusion therapy as well as additional supportive therapies [1][23][31][32].

Thus, there is a strong need for efficient and non-toxic therapeutic strategies due to the ongoing risk of cytopenia and resulting infections or bleedings as well as a known reduced QoL in patients with MAA.

One candidate for a therapeutic option seems to be thrombopoietin (TPO) which has a known effect on stem cells and progenitor cells [33]-[36]. The addition of recombinant TPO leads to an expansion of the hematopoietic stem cells pool in culture and the binding of TPO to the receptor c-MPL on megakaryocytes results in platelet maturation and release [33]. c-MPL is expressed on the surface of hematopoietic stem cells and progenitor cells [33]. Remarkably, in TPO knockout mice, beside low platelet count, a low number of stem cells and a poor stem cell function were found [34]-[36].

TPO, therefore seems to be not only a regulator of platelet production but a more general regulator of hematopoiesis.

Eltrombopag is an oral TPO mimetic that binds to c-MPL, promoting mega-karyopoiesis and release of platelets from mature megakaryocytes [37]. Eltrombopag increases platelet counts in healthy persons and is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) in splenectomized patients who are refractory to other treatments (e.g., corticosteroids, immunoglobulins). Eltrombopag may be considered as second-line treatment for adult non-splenectomized patients where surgery is contraindicated. Eltrombopag is also indicated for treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy and is under development for the treatment of a variety of additional disorders associated with thrombocytopenia, including Myelodysplastic Syndromes (MDS)/Acute Myeloid Leukemia (AML) related thrombocytopenia and chemotherapy-induced thrombocytopenia [37][38]. Eltrombopag was approved for use in refractory ITP in the United States in 2008 and in Europe in 2010. No increased risk for adverse events (AEs) during long-term treatment was seen in this patient group.

Eltrombopag was approved for SAA refractory to immunosuppressive therapy by the Food and Drug Administration (FDA) in 2014 and the European Medicines Agency (EMA) in 2015. This decision was based on long-term data regarding the safety and efficacy of a phase II study in SAA patients. This phase II study investigated eltrombopag as single agent treatment in patients with AA refractory to immunosuppressive treatment with ATGAM® / CSA [39]. In this study, 44% of patients had a hematological response in at least one lineage at 12 weeks. Some patients even achieved bi- or trilineage response. The increase in blood counts, in particular platelet count, occurred over several months, i.e. in AA patient's kinetics of response to eltrombopag was delayed compared to patients with immune thrombocytopenia. And AA patients need significantly higher dosages of eltrombopag (in most cases 150 mg per day) for a response. In other patient groups (e.g., MDS) daily dosages of 300 mg were tolerated without safety concerns [40][41]. Especially, no increased risk for the occurrence of MDS and AML was observed during the follow-up of 83 patients with refractory SAA and eltrombopag treatment [42]. Factors that predicted a response to eltrombopag were less depressed baseline reticulocytes and immature platelet count. This may reflect residual stem cells which can

respond to eltrombopag [39]. If this is true, the chance for response might be even better in MAA which is characterized by a less depleted stem / progenitor cell compartment compared with SAA/VSAA. Eltrombopag was well tolerated [39]. Furthermore, there was no hint for an additive toxicity, especially hepatotoxicity, by the addition of eltrombopag to standard intensified immunosuppression (hATG+CSA) [42]-[47].

Recent data of a combination therapy with intensified immunosuppressive therapy (hATG+CSA) and eltrombopag in first-line SAA and VSAA without the option of stem cell transplantation showed a significant benefit for the addition of eltrombopag to hATG+CSA without an increase in AEs [44]. Based on this data, eltrombopag was approved by the FDA in 2018 for first-line treatment of SAA/VSAA in combination with intensified immunosuppressive therapy.

This data raises also the hope for thrombopoetin as an effective new therapeutic option in patients with MAA.

It was hypothesized that there might be a higher rate of patients responding to eltrombopag in a group of therapy-naïve patients, especially in MAA. Furthermore, it was assumed that the addition of eltrombopag to the routinely used immunosuppression might lead to a further increase in remission rates. Thus, there is a strong need for more data regarding efficacy and tolerability of eltrombopag in AA in order to clarify the role of eltrombopag within standard treatment of AA, especially in MAA [48][49].

There is several data suggesting that telomere length and mutations of the telomerase complex are possible biomarkers for prognosis in AA patients. Telomere length (TL) reflects and limits the replicative lifespan of normal somatic cells, it thereby functions as a “mitotic clock”. Telomere erosion can be counteracted by the enzymatic activity of telomerase, a reverse transcriptase embedded into the so-called “shelterin” complex. Patients with adult bone marrow failure syndromes (BMFS) are typically characterized by shortened telomere length (STL) in peripheral blood cells. Interestingly, it was demonstrated that in a sub-population of these patients even more accelerated telomere attrition can be detected. It is suspected that this is due to cell-intrinsic, genetic alterations in underlying hematopoietic stem cells, e.g. due to inherited or acquired mutations in genes relevant for proper function of telomerase, ultimately leading to impaired telomere maintenance [50]-[52].

However, there is greater knowledge regarding pathophysiology and treatment of AA than knowledge of its psycho-social issues. QoL evaluation tools used in all studies for AA are rather unspecific and were initially designed for cancer patients (e.g. the EORTC QLQ-C30). Given the complexity of AA, the variation in symptoms and different treatment approaches and the fact that marrow failure syndromes are not classified as malignant diseases, it is likely that the cancer specific questionnaires used so far are inappropriate to adequately assess the QoL and illness intrusiveness in these patients. Based on these considerations and supported by German support groups (Aplastische Anämie-PNH e.V.) the development of an AA/PNH-specific QoL-instrument (QLQ-AA/PNH) was initiated. This QLQ-AA/PNH was performed according to EORTC QoL group guidelines, i.e. after identification of QoL issues by literature review, a focus group of patients and health care professionals were interviewed (phase I). After screening of documented interviews, QoL issues were generated and re-worded in a preliminary questionnaire (phase II). In phase III, the questionnaire with generated items was tested in a representative patient group and a psychometric validation of the final questionnaire was carried out [53]. As important QoL aspects of AA patients are inappropriately captured

with available EORTC-QoL tools, the development of a specific QoL tool was supported by evaluating the QLQ-AA/PNH in context of this trial.

## 7.2 Risk benefit assessment

There is a lack of efficient therapeutic options with tolerable toxicity profiles for patients with AA (especially elderly patients or patients with MAA). Due to lack of treatments with few side effects, the current treatment policy for this group of patients often comprises only supportive therapies. Thus, there is a strong need for efficient and non-toxic therapeutic strategies due to the risk of cytopenia and resulting infections or bleedings as well as a known reduced QoL in patients with MAA.

The TPO receptor agonist eltrombopag is an approved drug for adult ITP and for treatment of thrombocytopenia in patients with chronic hepatitis C and for SAA/VSAA refractory to immunosuppressive therapy (as well as for first-line use in the US). The approval of eltrombopag for the treatment of refractory SAA in adult patients who are not eligible for allogeneic stem cell transplantation was based on long-term data regarding to safety and efficacy of a recently published phase II study [43]. This study investigated eltrombopag as single agent treatment in patients with AA refractory to immunosuppressive treatment with ATGAM® / CSA. 44% of patients had a hematological response in at least one lineage at 12 weeks. Eltrombopag was well tolerated. Some patients even achieved bi- or trilineage response. The increase in blood counts, in particular platelet count, occurred over several months, i.e. in AA patients kinetics of response to eltrombopag was delayed compared to patients with immune thrombocytopenia. Factors that predicted a response to eltrombopag were less depressed baseline reticulocytes and immature platelet count. This may reflect residual stem cells which can respond to eltrombopag. If this is true, the chance for response might be even better in MAA which is characterized by a less depleted stem / progenitor cell fraction. Additionally, it was hypothesized that there might be a higher rate of patients responding to eltrombopag in a group of therapy-naïve patients with MAA.

The risk of AEs and unwanted side effects was assessed as containable because the drug was well tolerated in several studies regarding eltrombopag in refractory and primary SAA/VSAA [42]-[47]. Especially no increased risk for the occurrence of MDS and AML was shown during the follow-up of 92 previously untreated and 83 refractory SAA patients treated with eltrombopag [42][44][47].

Response data of a prospective trial including 92 previously untreated SAA and VSAA patients without the option of stem cell transplantation showed a significant benefit for the addition of eltrombopag to the standard immunosuppression with hATG+CSA [44]. Furthermore, there was no hint for an additive toxicity, especially hepatotoxicity, by the addition of eltrombopag to standard intensified immunosuppression [44]. These data resulted in the approval of eltrombopag for first-line treatment of SAA/VSAA in the US by the FDA in 2018.

Additionally, no AEs were seen during long-term treatment in refractory ITP in which eltrombopag was approved for use in 2008 in the US and 2010 in Europe.

A bone marrow analysis and regular blood testing is necessary in the diagnosis and treatment of patients with MAA. Thus, in most cases only a slightly larger amount of blood but no additional sampling was necessary in this study. This was especially true as sampling took often place in context of routine testing of the patients. The most relevant risks of venipuncture and bone marrow puncture are bleedings, infections and nerval lesions. In conclusion, the

additional risk due to study-related examinations (venipuncture and bone marrow puncture) was assessed as acceptable in comparison with the potential benefits.

Thus, the possible benefit of eltrombopag as a new therapeutic option in patients with AA clearly overweighed the potential risk of this treatment. Finally, this study was needed in order to clarify the role of eltrombopag within standard treatment of AA, especially in MAA.

# 8 Study objectives

The aim of this study was to improve treatment of MAA by evaluating the safety and efficacy of eltrombopag as a new treatment option in patients with MAA who received CSA as background treatment according to current practice.

The primary objective was the analysis of the hematologic response rate (partial response [PR] + complete response [CR]) at 6 months. Additional objectives were the evaluation of OS, FFS, response rate, time to best hematological and single lineage response, transfusion requirement, relapse rate, cumulative incidence of progress, toxicity profile as measured using the CTCAE criteria, QoL assessment and telomere lengths and telomerase mutations as biomarkers for response and in a subgroup of patients pharmacokinetic assessment of dose-dependency regarding efficiency and safety of eltrombopag.

# 9 Investigational plan

A copy of the last version of the CSP is provided in Appendix 16.1.1. The sample blank case report form (CRF) can be found in Appendix 16.1.2. Documents specifying the statistical analysis of this study are given in Appendix 16.1.9.

## 9.1 Description of overall study design

A summary of the study design is given in Figure 2.

This was a prospective, randomized, placebo-controlled, two-armed, double-blind multicenter study. Patients were randomized to receive either eltrombopag or placebo on top of the standard background therapy with CSA.

The study involved a total of 9 participating sites across Germany, Switzerland and France. It was planned to include 90 patients. For actual number of patients see Section 10.1.

After enrollment the patients were randomized either to the Placebo or Eltrombopag Arm (refer to Section 9.3.5). The randomization was double-blinded. All patients received background therapy with CSA.

Results of the 6 months evaluation (visit Va) were reported by sending the completed unblinding form to the trial office. For definition of CR and PR see Section 9.4.8.

After the initial treatment in the Placebo or Eltrombopag Arm, treatment was unblinded and patients allocated to different treatment groups according to the results of the response assessment at 6 months after start of therapy (see Figure 2).

**Group A)**

Patients in the Placebo Arm with no CR (i.e. PR or no response) at visit Va (6 months after start of study treatment):

1 Treatment with CSA was continued

2 Start of eltrombopag treatment 150 mg per day after confirming the diagnosis of MAA by a bone marrow examination and cytogenetic analysis

3 Depending on the results of the response assessment at visit VIIa, the patient was grouped to either Group A1 or Group A2

4 The study treatment was stopped at any time during the study, in case of progression to SAA or VSAA or MDS

**Group A1)**

Patients in Group A with no CR or PR (i.e. no response) at evaluation at visit VIIa (12 months after start of study treatment = 6 months treatment with eltrombopag)

1 End of treatment with eltrombopag

2 The decision regarding the further treatment of the patient belonged to the local physician

3 Evaluation and report of the remission status to the study office 12 and 18 months after start of study treatment

4 Follow-up visit with report of remission status 24 months after start of study treatment (24 months after visit IIa) but not later than 30 Jan 2025.

**Group A2)**

Patients in group A with CR or PR at the evaluation at visit VIIa (12 months after the start of study treatment = 6 months after the start of eltrombopag)

1 In case of CR, eltrombopag was tapered over 2 months as follows:

   => 50% of the last dose for the first month

   => in case of stable blood counts: reduction of eltrombopag intake to every second day for an additional month

   => in case of stable blood counts: stop of eltrombopag treatment

   In case of worsening of the blood counts during the tapering, eltrombopag was escalated to the dosage before decrease of the blood counts had started.

2 In case of a PR eltrombopag was continued or escalated until 12 months of eltrombopag treatment or CR was reached. Following this, eltrombopag was tapered over 2 months as described in point number 1 above.

3 Slow tapering of CSA (after a minimum of 12 months of CSA treatment unless AEs (e.g. impaired renal function) requiring an earlier reduction or stop of CSA occurred.

   - CSA should not have been reduced simultaneously with the dose reduction or the stop of eltrombopag.
   - Dose reduction of CSA should have been delayed until at least 8 weeks after reduction or stop of eltrombopag.

4 End of treatment with eltrombopag 18 months after therapy start (i.e. 12 months of eltrombopag treatment) with slow tapering of eltrombopag over a period of 2 months as described in point 1 above.

5 In case of relapse after eltrombopag reduction or stop before reaching 12 months of eltrombopag treatment, a restart of eltrombopag within the EMAA study was possible.

6 In case of relapse after the end of the treatment phase (Visit VIII), a restart of eltrombopag should have been considered as an off-study treatment.

7 Eltrombopag could not be provided as study drug after 14 months (including tapering) of eltrombopag treatment within the EMAA study.

8 Evaluation and report of the remission status to the study office 12 and 18 months after start of study treatment.

9 Follow-up visit with report of the remission status 24 months after start of study treatment (24 months after visit IIa) but not later than 30 Jan 2025.

**Group B)**

Patients in the Placebo Arm with CR at visit Va (6 months after therapy start):

1 End of treatment with placebo (6 months after therapy start).

2 Ongoing CSA treatment. Slow tapering of CSA (after a minimum of 12 months of CSA treatment unless AEs (e.g. impaired renal function) requiring an earlier reduction or stop of CSA occurred.

3 Follow-up visit with report of the remission status 24 months after start of study treatment (24 months after visit IIa) but not later than 30 Jan 2025.

**Group C)**

Patients in the Eltrombopag Arm with CR or PR at visit Va (6 months after therapy start)

1 In case of CR, eltrombopag was tapered over 2 months as follows:

   => 50% of the last dose for the first month

   => in case of stable blood counts: reduction of eltrombopag intake to every second day for an additional month

   => in case of stable blood counts: stop of eltrombopag treatment

   => In case of worsening of the blood counts during the tapering, eltrombopag was escalated to the dosage before decrease of the blood counts had started.

2 In case of a PR without reaching a trilineage response with a platelet count remaining < 70 G/L eltrombopag should have been continued or escalated until 12 months of eltrombopag treatment or CR was reached. A dose escalation could have been considered after consulting the Coordinating Investigator. Following this, eltrombopag should have been tapered over 2 months as described above. Slow tapering of CSA after a minimum of 12 months of CSA treatment unless AEs (e.g. impaired renal function) requiring an earlier reduction or stop of CSA occurred.

   - CSA should not have been reduced simultaneously with the dose reduction or the stop of eltrombopag.
   - Dose reduction of CSA should have been delayed until at least 8 weeks after reduction or stop of eltrombopag.

3 End of treatment of eltrombopag 12 months after therapy start (i.e. 12 months

eltrombopag treatment) with slow tapering of eltrombopag over a period of 2 months.

4 In case of relapse after eltrombopag reduction or stop before reaching 14 months (including tapering) of eltrombopag treatment, a restart of eltrombopag within the EMAA study was possible.
5 In case of relapse after the end of the trial treatment phase (Visit VIII), a restart of eltrombopag should have been considered as an off-study treatment.
6 Eltrombopag could not be provided as study drug after 14 months (including tapering) of eltrombopag treatment within the EMAA study.
7 Evaluation and report of the remission status to the study office 12 and 18 months after start of study treatment
8 Follow-up visit with report of remission status 24 months after start of study treatment (24 months after visit IIa) but not later than 30 Jan 2025.

**Group D)**

Patients in the Eltrombopag Arm with no CR or PR (i.e. no response) at 6 months after therapy start:

1 End of treatment with eltrombopag (6 months after therapy start).
2 Decision regarding further treatment belonged to the local physician.
3 Evaluation and report of the remission status to the study office 12 and 18 months after start of study treatment.
4 Follow-up visit with report of remission status 24 months after start of study treatment (24 months after visit IIa) but not later than 30 Jan 2025.

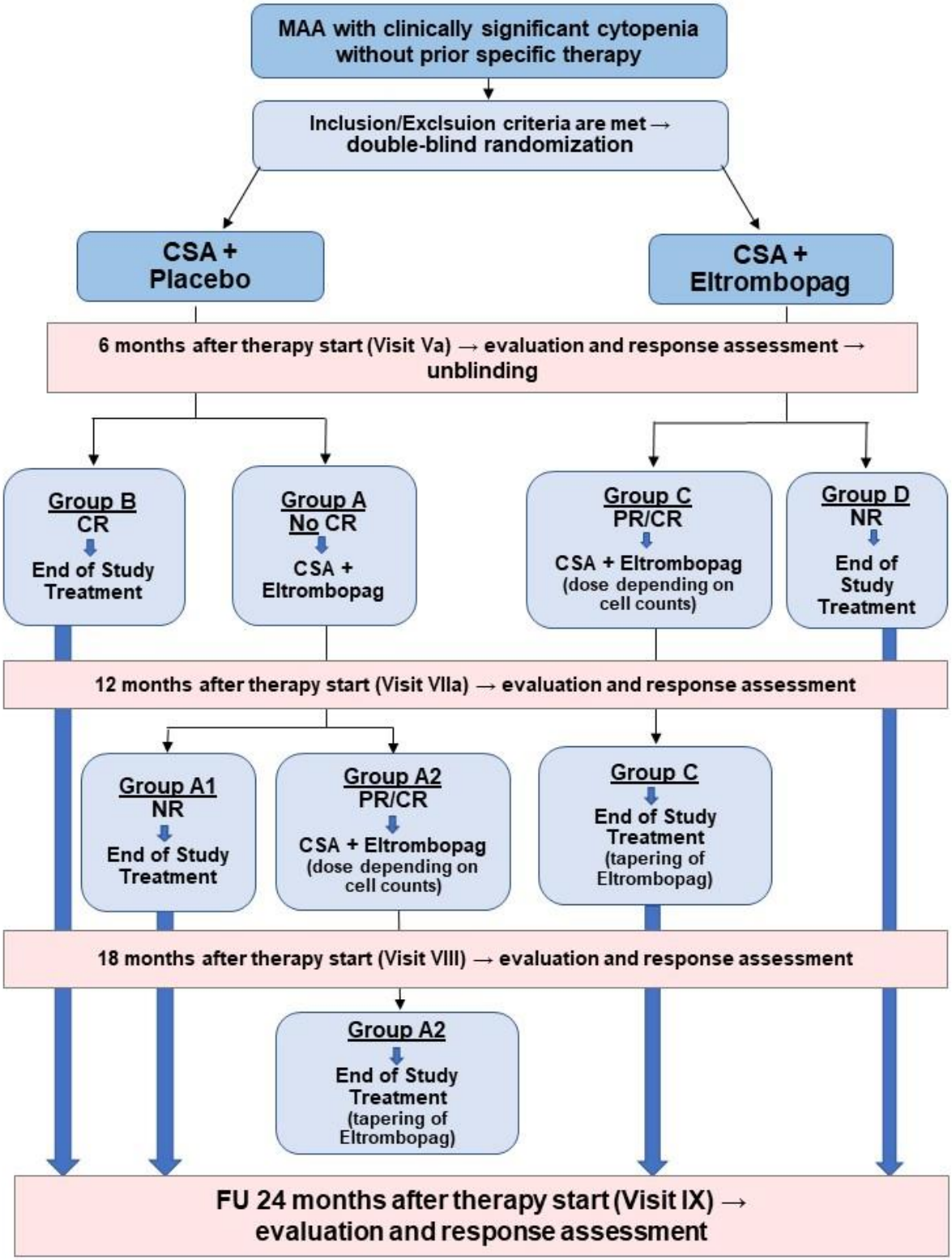
Briefly summarized, patients received eltrombopag or placebo within the study for a minimum of 6 months. Exceptions are patients with disease progression in SAA or VSAA or patients with inacceptable AEs within the first 6 months.

Eltrombopag was administered for a maximum period of 12 months + tapering period within the protocol. Recent data showed that the response of hematopoiesis in refractory SAA could be sustained on discontinuation of eltrombopag [43].

As long-term effects of investigational treatments were an objective of the study, the follow-up of patients for all groups covered 24 months after the start of the study treatment (24 months after visit IIa) or until the end of the study, whatever occurred first.

After the end of study, the patients were examined and treated by their local physicians. The study drug was generally not provided after the end of the study.

**Figure 2: Trial flowchart**



### 9.1.1 Justification of study design

For background information and study objectives see Sections 7.1 and 8.

### 9.1.2 Justification of dosing regimen

A phase II study in patients with refractory AA started with an initial dose of 50 mg/day and increased the daily dose by 25 mg every two weeks in non-responding patients to a maximum of 150 mg. This trial demonstrated that most responding patients achieved responses without increase of AEs only after increase of the eltrombopag dose to 150 mg/day [39] which therefore became the recommended dose for treatment of AA used in subsequent trials [54] and is the recommended dose in the FDA approval for treatment of SAA and the EMA approval for refractory AA.

### 9.1.3 End of the clinical study

As for this study, the primary outcome was analyzed after the last patient had completed the follow-up phase (24 months after start of study therapy but not later than 30 Jan 2025). Thus, the end of the study was the date when the clean database was available. However, the primary completion event of the study was the date of last patient last visit (LPLV).

In agreement with the protocol the recruitment was closed because of low enrollment rate in June 2023.

## 9.2 Selection of study population

### 9.2.1 Justification for selection criteria and gender selection

The selection criteria were chosen to ensure that subjects with specific risks for administration of the study medication and / or subjects with conditions which might have had an impact on the aims of the study were excluded. Male and female subjects were included in the present study representing the population of patients suffering from MAA without relevant gender prevalence.

### 9.2.2 Inclusion criteria

Subjects had to meet the following criteria to be eligible for the study:

1 Current diagnosis of MAA requiring standard treatment with CSA without prior specific therapy.

MAA was defined as AA fulfilling the following criteria:

- no evidence of other disease-causing marrow failure.
- hypocellular bone marrow for age.
- depression of at least two out of three peripheral blood counts below the normal values in two different blood samples in a time span from at least two weeks:
  - absolute neutrophil count (ANC) < 1.2 G/L
  - platelet count < 70 G/L
  - absolute reticulocyte count < 60 G/L [55]

without fulfilling the criteria for SAA (hypocellularity of bone marrow 25% and depression

of two of the three peripheral counts: ANC < 0.5 G/L, platelet count < 20 G/L, reticulocyte count < 20 G/L) [55]

2 In this study need for treatment with CSA was defined as:

2a) **transfusion-independent MAA and**:

- ANC < 1.0 G/L
- or hemoglobin < 8.5 g/dl and reticulocyte count < 60 G/L
- or platelet count < 30 G/L
- or significant clinical symptoms (infections, bleeding, anemia)

2b) **transfusion-dependent MAA:**

- Platelet transfusion dependency was defined as prophylactic transfusion (platelet counts < 10 G/L with no bleeding) or therapeutic transfusion in the 12 weeks prior to study entry
- Red cell transfusion dependency was defined as transfusion of at least 4 units of pRBC in the 12 weeks prior to study entry

3 A signed and dated informed consent was necessary before the conduct of any study-specific procedure.

### 9.2.3 Exclusion criteria

Subjects were excluded from the study if they displayed any of the following criteria:

1 Age < 18 years
2 Constitutional AA (Fanconi anemia or Dyskeratosis congenita)
3 Clonal myeloid disorders based on cytogenetic findings performed within 12 weeks of study entry. Especially, patients with cytogenetic abnormalities which were recurrent in MDS (-7 or del(7q), del(5q)/5q loss, i(17q) or t(17p), -13 or del(13q), del(11q), del(12p) or t(12p), del(9q), idic(X)(q13), t(11;16)(q23.3;p13.3),t(3;21)(q26.2;q22.1), t(1;3)(p36.3;q21.2), t(2;11)(p21;q23), inv(3)(q21.3q26.2)/t(3;3)(q21.3;q26.2), t(6;9)(p23;q34)) [56] were not eligible for the study.
4 Bone marrow reticulin fibrosis of grade 3 or greater
5 Severe concurrent diseases precluding the patient's ability to tolerate protocol therapy
6 ALT > 3 times the upper limit of normal (ULN) if this elevation was progressive, or persistent for 4 weeks, or accompanied by increased direct bilirubin, or accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation
7 Infection not adequately responding to appropriate therapy
8 HIV-positivity (patients with Hepatitis B- or Hepatits C-positivity were only in combination with hepatic failure (see criteria 7) excluded)
9 Moribund status with a likely death within 3 months
10 History of malignancy other than localized tumors diagnosed more than one year previously and treated surgically with curative intent (for instance squamous cell or other skin cancers, stage 1, breast cancer in situ, cervical carcinoma in situ).
11 Prior specific treatment of AA with immunosuppression or androgens or interleukin 2-receptor-antibodies. The use of these drugs in context of other disorders before diagnosis of AA was not an exclusion criterion if these treatments were finished longer than 6 months before study entry.
12 Treatment with other hematological effective drugs (including erythropoietin) within

3 months before study entry as well as treatment with corticosteroids and G-CSF within 3 weeks before enrollment
13 Known hypersensitivity to eltrombopag or its components
14 Known hypersensitivity to CSA
15 Current nursing, pregnancy, or unwillingness to take oral contraceptives or use a barrier method of birth control to refrain from pregnancy as well as a missing or positive pregnancy test within the last 14 days before inclusion for women with childbearing potential during the course of this study.
16 Inability to understand the investigational nature of the study or to give informed consent.
17 Renal failure with creatinine > 2 x ULN.
18 Uncontrolled hypertension.
19 Participation in any study using an investigational drug or treatment with an investigational drug within 30 days preceding the first dose of study medication.

### 9.2.4 Discontinuation of treatment for individual patients

In individual patients the study treatment was to be interrupted in case of:

- Non- thrombocytopenia-related bleeding
- Increase of platelets > 450 G/L (increase of platelet counts > 150 G/L in patients with history of or risk factors for thromboembolism)
- Drop of ANC > 30% of the latest zenith value (with ANC < 500/µL), in those subjects who during treatment had increased their ANC of > 30% from baseline values
- At occurrence of an SAE if it became necessary for medical reasons
- Increase of ALT > 3.0 x ULN in patients with normal liver function, in patients with increased ALT before start, an increase of ALT ≥ 3.0 x of the start value/alternatively > 5 x ULN (the lower value was to be chosen) combined with:
    - an elevation of bilirubin > 2.0 x ULN (without an accompanying disorder of the biliary tract
    - or elevation of alkaline phosphatase > 2 x ULN (Hy's Law)
    - or clinical symptoms indicating a liver injury or hepatic decompensation
    - or persistence for 4 weeks

In addition, in individual patients the study could have been stopped in case of progression of the disease to have the opportunity to start with more aggressive treatment schedules like intensified immunosuppression or stem cell transplantation.

After the end of study, the patients were examined and treated by their local physicians. The study drug is not offered after the end of study.

### 9.2.5 Withdrawal and drop-out

The study participants could always terminate the study without explanation. Any patient enrolled into the protocol, who was withdrawn at any time for any reason before the last follow-up visit (24 months after end of study treatment) was considered an early withdrawal and was not replaced. A complete set of data including the reason for withdrawal was collected on every patient up to the time of withdrawal from the study. All information prior to the withdrawal from the study was used for the analysis. No further information and material were collected about

the patient after the time of withdrawal from the study. Regardless of the reasons for discontinuing study treatment, patients should have been followed up for a minimum of 30 days after the last dose of IMP, in order to obtain safety data.

The investigator should have withdrawn a patient from the study treatment whenever continued participation was no longer in the patient's best interests. Reasons for discontinuing treatment might have included the occurrence of an SAE or an intercurrent illness, patient's own request to end treatment, or significant uncertainty.

A patient could have decided at any time that he/she no longer wanted to continue in the trial. In this event, the investigator should have tried to establish the reason why the patient no longer wanted to participate in the trial and asked for the consent to collect data regarding patient survival and remission status information at 6 months, 12 months, 18 months and 24 months after study start.

If a patient was prematurely withdrawn from the trial the investigators should as a minimum, have made reasonable attempts to collect safety data up to a minimum of 30 days after the last dose of IMP. Efforts should also have been made to obtain the patient´s survival and remission status information at 6 months, 12 months, 18 months and 24 months after study start.

Details for the premature termination of the whole study are provided in Section 9.7.

### 9.2.6 Subject identification

Following the informed consent procedure, the trial site registered eligible patients for the study by assigning a unique study-specific patient ID. This patient ID was composed of a two-digit country code followed by a two-digit trial site number, followed by a three-digit number in ascending order. Every registered patient retained this Patient ID regardless of whether the patient was a screening failure after checking all inclusion and exclusion criteria or whether the patient was included in the study.

## 9.3 Treatments

### 9.3.1 Treatments administered

Patients were randomly assigned to either the Placebo or Eltrombopag Arm. After the initial treatment in the Placebo or Eltrombopag Arm, treatment was unblinded and patients allocated to different treatment groups according to the results of the response assessment at 6 months after start of therapy (see Figure 2 and Section 9.1)

All patients received background therapy with CSA as described in Section 9.3.2.2.

### 9.3.2 Dosing

#### 9.3.2.1 Eltrombopag

Eltrombopag (or placebo) was given at a daily starting dose of 150 mg orally as 75 mg tablets once daily (2 tablets eltrombopag 75 mg or placebo per day) [39]. The tablets could have been taken at any time of the day. However, the patients had to allow at least a 4-hour interval between the investigational drug and other medications (e.g., antacids), calcium-rich foods (e.g., dairy products and calcium fortified juices), or supplements containing polyvalent cations

such as iron, calcium, aluminum, magnesium, selenium, and zinc. Patients were thoroughly informed about this necessary procedure. Otherwise, stable and efficient plasma levels could not be guaranteed.

In Asian patients, eltrombopag (or placebo) was given at a daily starting dose of 75 mg orally (1 tablet eltrombopag or placebo per day). In Asian-Caucasian patients, no dose reduction of the starting dose was necessary, but cautious observation of the liver function due to the possibility of altered eltrombopag metabolism was recommended.

**Dose escalation**

There was an option of dose escalation to 225 mg eltrombopag per day after 6 months of eltrombopag treatment without reaching CR in group A2 and C:

- after consulting the Coordinating Investigator
- if no trilineage response occurred
- and the platelet count remained < 70 G/L
- and there were no signs of dysplasia in a microscopic blood count within 1 week before dose escalation and in the bone marrow within 14 weeks before dose escalation
- and the confirmation of the absence of AEs possibly or definitely related to the study drug based on the assessment of the investigator
- and informed consent of the patient to participate in the pharmacokinetic study, which was obligate in cases of dose escalation

**Dose reduction and stop of eltrombopag**

1 In patients **without** history of thromboembolism or known risk factors for thromboembolism, dose reduction (the possibility of an alternating dose schedule was given) was recommended, if the platelet count reached > 150 G/L. Regular blood count controls were necessary during dose reduction.

   - Dosage should have been decreased to achieve a platelet count between 100 and 150 G/L after reaching an erythrocyte and granulocyte response (PR or CR).
   - If the platelet count decreased below 100 G/L, the eltrombopag dose should have been escalated again.
   - Eltrombopag should have been discontinued, if the platelet count exceeded 450 G/L and could have been restarted with a lower dose after decrease of the platelet count below 150 G/L.

2 In patients **with** history of thromboembolism or known risk factors for thromboembolism (e.g. Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, PNH with GPI-deficient granulocyte population > 50 % or LDH > 1.5 x ULN, prolonged periods of immobilization, contraceptives and hormone replacement therapy or surgery), dose reduction was recommended if the platelet count reached > 100 G/L. Regular blood count controls were necessary during dose reduction.

   - The target platelet count was 70 - 120 G/L for this group of patients after reaching an erythrocyte and granulocyte response (PR or CR).
   - If the platelet count decreased below 70 G/L, the eltrombopag dose should have been escalated again.
   - Eltrombopag should have been discontinued in this group of patients if the platelet count exceeded 150 G/L.

In cases of eltrombopag stop according to the protocol the dose should have been reduced to 50% of the last dose per day for 4 weeks, followed by reduction of the eltrombopag intake to every second day for additional 4 weeks.

**Dose reduction of Eltrombopag in case of liver function abnormalities**

Eltrombopag should have been discontinued in patients with normal liver function if alanine aminotransferase (ALT) levels increased 3 x ULN or in patients with an elevated ALT prior to treatment if ALT levels increased ≥ 3.0 x the starting value before treatment or alternatively > 5 x ULN (whichever value was lower) combined with:

- progression or
- persistence for 4 weeks, or
- increased direct bilirubin > 2.0 x ULN (without an accompanying disorder of the biliary tract or
- elevation of alkaline phosphatase > 2 x ULN (Hy's Law) or
- clinical symptoms of liver injury or evidence for hepatic decompensation like jaundice, ascites, diminished protein synthesis such as albumin, hormones and clotting factors.

In the event of an increase in the ALT level to > 6 x ULN, subjects were to return to clinic or have blood tests drawn by the home physician every 3-4 days. If ALT remained > 6 x ULN on a second blood test, eltrombopag was to be discontinued until ALT was ≤ 3 x ULN.

Eltrombopag could have been restarted at a lower dose than the prior dose after ALT was < 3 x of ULN. If liver test abnormalities returned to an ALT level > 6 x ULN, eltrombopag dose should have been reduced until there was a reduction of ALT < 3 x of ULN.

No dose adjustment of eltrombopag was necessary in patients with renal impairment. Patients with impaired renal function should have used eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis.

### 9.3.2.2 Ciclosporin A

According to European guidelines [11][12][23][28]-[30] CSA was administered orally with an initial daily dose of 5 mg/kg/day divided into two doses. Then, dosage should have been adjusted with the aim of a trough CSA blood level of 200 - 400 ng/mL (using a polyclonal assay) or 150 - 250 ng/mL (using a monoclonal assay).

CSA is the standard medication for this indication and was therefore not provided as a study medication. Handling and monitoring of CSA levels were performed as recommended.

It was recommended that the CSA treatment was taken at a full dose for 12 months under continued serum level and clinical monitoring. If CR was achieved, CSA should have slowly been reduced by the next 6–12 months. In case of stable blood counts, the treatment was tapered about 5–10% of the daily dose every month [23]. In case of decrease of the blood counts after dose reduction, the dose should have been increased again. Dose reduction of CSA should have been delayed until at least 8 weeks after reduction or stop of eltrombopag. In case of AEs (e.g. impaired renal function), CSA could have been reduced or stopped at the discretion of the investigator.

The CSA dose was to be reduced to the maximum tolerated dose in case of significant negative side effects (for example renal insufficiency).

### 9.3.3 Selection of doses in the study

For dosing of eltrombopag see Section 9.3.2.1.

### 9.3.4 Drug logistics, storage and accountability

The study sites received labeled eltrombopag or placebo. The active tablets contained eltrombopag olamine equivalent to 75 mg and present as white, round, film-coated tablets.

The presentation of the placebos matched the active tablets as white round film-coated tablets and contained no Eltrombopag olamine equivalent.

Labels were prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. Label text was approved according to the sponsor's procedures and a copy of the labels is provided in the trial master file (TMF).

A complete record of batch numbers and expiry dates of all study treatment is maintained in the TMF.

The IMP was stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the IMP were limited to the investigator and authorized site staff. The IMP was dispensed or administered only to subjects enrolled in the study and in accordance with the protocol. The IMP had to be stored at room temperature. There was no special handling and storage requirement for the IMP.

Accountability for the trial IMP at the trial site was the responsibility of the Principal Investigator (PI). The PI could delegate the responsibility of receipt, dispensing and destruction, as applicable, to the local pharmacist, or other appropriate personnel, however, this was to be written in the site's delegation of authority log. The PI or his delegates ensured that the trial drug was used only in accordance with this protocol.

Drug accountability records, maintained by the trial site, indicated:

- IMP stored at site (tracking number, lot number & batch number)
- use by each patient (including IMP name, lot number, batch number & tracking number)
- disposal of unused IMP or destruction of used IMP (date, lot number, batch number & tracking numbers)

The patient was asked if he or she was willing to be treated at every visit. The results as well as IMP disposal and return were documented.

### 9.3.5 Patient registration and randomization

The number of patients per site was not determined.

After informed consent, eligible patients were randomized into the study by completing the patient registration and randomization form.

Double blinding and randomization were the main measures within this protocol to avoid an unwanted bias of the study data. The aim of the patient registration and randomization form was to confirm eligibility and to assign the subjects to one of the two treatment arms: Eltrombopag or Placebo.

CSA was administered to each of the clinical trial subjects, regardless of randomization group, to treat MAA according to current standard of care.

All eligible patients who had signed the ICF and fulfilled all eligibility criteria were randomized using a central, stratified, block randomization process. The registration and randomization form contained site ID and patient screening ID und was signed by the PI or Co-Investigator listed on the staff delegation log.

Randomization was stratified by age and transfusion dependence or in-dependence. On receipt of the patient registration and randomization form, the patient data were entered in the Electronic Trial Data Base (eCRF). The assignment to either the standard (placebo) or the investigational treatment (eltrombopag) was done by an independent data manager to guarantee that the randomization was separated from the clinical investigators. The ratio of patients included in each arm for placebo versus eltrombopag treatment was 1:1.

Randomization took into account patient's age and disease severity by stratifying into 4 block combinations to ensure homogeneity between treatment arms, according to the following subgroups:

Disease severity (see inclusion criteria):

- transfusion-independent MAA
- transfusion-dependent MAA

and Age:

- 18 - 60 years old
- > 60 years old

| | |
|---|---|
| Block 1: transfusion-independent MAA<br>18-60 years old | Block 2: transfusion-independent MAA<br>> 60 years old |
| Block 3: transfusion-dependent MAA<br>18-60 years old | Block 4: transfusion-dependent MAA<br>> 60 years old |

There was no randomization or preference regarding the gender planned. As AA is not a gender-dependent disorder, a balanced gender distribution was expected.

The site received a registration/randomization confirmation containing:

- a unique subject number (Pat-ID) which identified the patient during the study
- and the numbers (Med-No.) of the medication boxes assigned to the patient.

The study site dispensed the allocated medication boxes to the patient and documented date, time and Med-No. of the allocated boxes in the eCRF.

After 6 months of treatment within the study as well as completing and documentation of the 6 months assessment at visit Va, the individual patient was unblinded by the study office by completing the unblinding Form. The site received the information whether the patient, who was identified by the patient ID, received placebo or eltrombopag.

### 9.3.6 Blinding

Treatment with placebo or eltrombopag in the first 6 months after study start was double-blinded.

To maintain the overall quality and legitimacy of the clinical trial, code breaks should have occurred only in exceptional circumstances when knowledge of the actual treatment was absolutely essential for further management of the patient.

The Investigator was encouraged to maintain the blinding process as much as possible. The actual allocation was not to be disclosed to the patient and/or other study personnel nor should there have been any written or verbal disclosure of the code in any of the corresponding patient documents.

The Investigator had to report all code breaks (with reason) as they occurred on the corresponding eCRF page.

The occurrence of AEs or SAEs should not necessarily have caused an unblinding. Unblinding should not necessarily have been a reason for study drug discontinuation.

Code break envelopes were delivered with the allocated medication boxes. For each medication box, a code break envelope was provided. The individual receiving the code breaks

- Signed and dated the delivery documentation to acknowledge receipt of the code break envelopes.
- Filed the delivery documentation in the relevant section of the ISF. This form was also required to document return of code break envelopes to the CRO at the end of the study.
- The person receiving the code break envelopes signed and dated the form to document that he/she has taken responsibility for the code break envelopes received.
- Code break envelopes distributed by the CRO were returned to the CRO following completion of the trial but prior to study close down.

The unblinding which was allowed during the conduct of the EMAA trial after the 6 months evaluation was **NOT** done by the sites!

To protect the integrity of the study, it was to be ensured that no unnecessary or unintentional unblinding occurred.

It might have been necessary to break a trial code for the following reasons:

- in the event of a medical emergency in a trial participant and by request from the physician responsible for the patient or the CI/PI for the trial
- in the event of a Serious Adverse Drug Reaction (SADR) or a Suspected Unexpected Serious Adverse Reaction (SUSAR) in a trial participant and by request from the Sponsor
- in the event of concerns about trial safety (e.g. for review by the DSMB) and by request from the Sponsor.

It had to be documented who broke the code and when and why it happened. This information was to be filed in the ISF. The PI was responsible for documenting the breaking of the code and the reasons for doing so in the eCRF and in the ISF.

The results of the code break were to be communicated only to the Sponsor and not to any member of the investigative team in order to protect the integrity and validity of the data.

The PI was responsible for notifying the study office immediately that a code had been broken. There it was to be checked that all necessary parties, including Research Ethics Committee were aware of the code break.

### 9.3.7 Prior and concomitant therapy

All prior and concomitant medications were documented and reported in the eCRF.

For restricted previous and/or concomitant medication please refer to Section 9.2.3, exclusion

criteria.

During treatment with CSA, vaccination might be less effective, and the use of live attenuated vaccines should have been avoided.

Potential interactions of eltrombopag and CSA with food and comedications were listed in the CSP and recommendations given for monitoring of side effects and dose adaptations.

### 9.3.8 Treatment compliance and drug accountability

For assessment of patient compliance, patients entered daily administration of the study drug into their patient diary which remained in the study center after the study was finished. Patients were instructed to bring all unused and empty packages of medication with them to each study visit to assess patient's compliance.

### 9.3.9 Post-study therapy

In this study, eltrombopag was only provided to trial patients for a maximum of 14 months. After the study treatment was completed, no further eltrombopag treatment was provided by the Sponsor but at the discretion of the treating physician patients could have received further eltrombopag treatment outside of this study.

## 9.4 Efficacy and safety variables

### 9.4.1 Efficacy and safety measurements assessed and flow chart

Specific time points for evaluation of efficacy variables and safety measures are given in the study flowchart (Table 11).

As shown in the tables below, the visit schedule was based on weeks. Visits to evaluate the endpoints after 3, 6, 12, and 18 months actually took place after 12, 24, 48, and 72 weeks. For simplicity and consistency with the terminology used in the CSP and SAP, months are used to refer to the evaluation time points in the following text. The schedule of visits in weeks can be found in the study flowchart below (Table 11).

The primary endpoint was evaluated at visit Va, scheduled 24 weeks after treatment start. In the following, this is referred to as the 6-month evaluation. The same applies to endpoints after 3 months (12 weeks) or 12 months (48 weeks).

## Table 11: Visit schedule and study-related measures

### All groups visit I - Va

| Visit | Ia | Ib | IIa | IIb | IIIa | IIIb | IVa | IVb | IVc | Va |
|---|---|---|---|---|---|---|---|---|---|---|
| | **pre-study** | **enrollment** | **Therapy start** | | | | | | | **evaluation** |
| Weeks after study treatment start | | | 0 | 2 | 4 | 8 | 12 | 16 | 20 | 24 |
| **In site** | | | | | | | | | | |
| Signed informed consent | x | | | | | | | | | |
| Study enrollment/randomization form | | x | | | | | | | | |
| Quality of Life instruments | x | | x | x | x | x | x | x | x | x |
| Clinical history | x | | | | | | | | | |
| Anamnesis | x | | x | x | x | x | x | x | x | x |
| Physical examination | x | | x | x | x | x | x | x | x | x |
| Transfusion history/number of transfused units | x | | | | | | x | | | x |
| Bone marrow biopsy and aspiration with cytogenetics [1,2] | x | | | | | | | | | x |
| Full blood count with WBC differential and reticulocyte count | x | | x | x | x | x | x | x | x | x |
| Microscopic peripheral blood count | x | | x | | x | x | x | x | x | x |
| Ferritin | | | x | | | | x | | | x |
| Blood chemistry | x | | x | x | x | x | x | x | x | x |
| ECG | x | | | | | | x | | | x |
| Ophthalmologic examination (cataract) | x | | | | | | | | | x |
| Drug dispensary/withdrawal | | | x | | x | | x | | | x |
| Evaluation response and decision of further treatment | | | | | | | | | | x |
| Dose reduction or stop of study treatment [3,4,6,7] | | | | | x[3] | x[3] | x[3] | x[3] | x[3] | x[3,4,6,7] |
| Decision of dose escalating[8,9] | | | | | | | | | | x group **C** |
| | | | | | | | | | | |
| **Out site, central laboratory** | | | | | | | | | | |
| GPI-AP-Flow cytometry | | | x | | | | | | | x |
| Telomeric analysis | | | x | | | | | | | x |
| Bone marrow preparations [1,2] | | | x | | | | | | | x |
| Pharmacokinetic (in case of dose escalation in group C) [8,9] | | | | | | | | | | x |

**Group A: no CR after 6 months CSA + placebo => Eltrombopag start**

| Visit | Va | Vb | Vc | Vd | VIa | VIb | VIIa |
|---|---|---|---|---|---|---|---|
| Weeks after study treatment start (Group A) | 24 | 26 | 28 | 32 | 36 | 42 | 48 |
| Weeks after Eltrombopag-start (Group A) | 0 | 2 | 4 | 8 | 12 | 18 | 24 |
| | | | | | | | |
| **In site** | | | | | | | |
| Quality of Life instruments | x | x | x | x | x | x | x |
| Anamnesis | x | x | x | x | x | x | x |
| Physical examination | x | x | x | x | x | x | x |
| Transfusion history/number of transfused units | x | | | | x | | x |
| Bone marrow biopsy and aspiration with cytogenetics [1,2] | x | | | | | | x [group A1] |
| Full blood count with WBC differential and reticulocytes | x | x | x | x | x | x | x |
| Microscopic peripheral blood count | x | x | x | x | x | x | x |
| Ferritin | x | | | | x | | x |
| Blood chemistry | x | x | x | x | x | x | x |
| ECG | x | | | | | | x |
| Ophthalmologic examination (cataract) | x | | | | | | x [group A1] |
| Drug dispensary/withdrawal | x | | | | x | | x |
| Evaluation of response, decision of further treatment | x | | | | | | x |
| Dose reduction or stop of study treatment [3,4,6,7] | x | | x[3] | x[3] | x[3] | x[3] | x[3,4,6,7] |
| | | | | | | | |
| **out site, central laboratory** | | | | | | | |
| GPI-AP-Flow cytometry | x | | | | | | x |
| Telomeric analysis | x | | | | | | x |
| Bone marrow preparations [1,2] | x[1,2] | | | | | | x [group A1] |

**Group A1: no PR after 24 weeks Placebo + CSA, followed by 24 weeks Eltrombopag + CSA => end of study treatment**

| Visit | VIIa | VIIb | VIII | IX |
|---|---|---|---|---|
| Weeks after study treatment start (Group A1) | 48 | 56 | 72 | 96 |
| Weeks after Eltrombopag start (Group A1) | 24 | 32 | 48 | 72 |
| **In site** | | | | |
| Quality of Life instruments | x | x | x | x |
| Physical examination | x | x | x | x |
| Anamnesis | x | x | x | x |
| Number of transfused units | x | x | x | x |
| Bone marrow aspiration and biopsy [1,2] | x | | | x |
| Cytogenetics | x | | | x |
| Full blood count with WBC differential | x | x | x | x |
| Microscopic peripheral blood count | x | x | x | x |
| Reticulocyte count | x | x | x | x |
| Ferritin | x | | x | x |
| Blood chemistry | x | x | x | x |
| ECG | x | | | x |
| Ophthalmologic examination (cataract) | x | | | x |
| Evaluation response and protocol failure | x | | x | x |
| | | | | |
| **Out site, central laboratory** | | | | |
| GPI-AP-Flow cytometry | x | | x | x |
| Telomeric analysis | x | | x | x |
| Bone marrow preparations [1,2] | x | | | x |

**Group A2: CR or PR after 24 weeks Placebo + CSA, followed by 24 weeks Eltrombopag + CSA => Eltrombopag dose depending on response**

| Visit | VIIa | VIIa[9] | VIIa[9] | VIIb | VIIb[9] | VIIc | VIII | VIIIa[GroupA2] | VIIIb[GroupA2] | IX |
|---|---|---|---|---|---|---|---|---|---|---|
| Weeks after study treatment start (Group A2) | 48 | 50 | 52 | 56 | 60 | 64 | 72 | 80 | 88 | 96 |
| Weeks after Eltrombopag start (Group A2) | 24 | 26 | 28 | 32 | 36 | 40 | 48 | 56 | 64 | 72 |
| **In site** | | | | | | | | | | |
| Quality of Life instruments | x | x | x | x | x | x | x | x | x | x |
| Physical examination | x | x[9] | x | x[9] | x | x | x | x[9] | x | x |
| Anamnesis | x | x[9] | x | x[9] | x | x | x | x[9] | x | x |
| Number of transfused units | x | | | | x | | | | x | x |
| Bone marrow biopsy and aspiration with cytogenetics [1,2,9] | x[2] | | | | | | | | | x |
| Cytogenetics | x[2] | | | | | | | | | x |
| Full blood count with WBC differential | x | x[9] | x | x[9] | x | x | x | x[9] | x | x |
| Microscopic peripheral blood count | x | x[9] | x | x[9] | x | x | x | x[9] | x | x |
| Reticulocyte count | x | x[9] | x | x[9] | x | x | x | x[9] | x | x |
| Ferritin | x | | | | x | | | | x | x |
| Blood chemistry | x | x[9] | x | x[9] | x | x | x | x[9] | x | x |
| ECG | x | x[9] | | x[9] | | | | x[9] | | x |
| Ophthalmologic examination (cataract) | x | | | | | | | | | x |
| Drug dispensary/withdrawal | x | | | | x | | | | x | x |
| Dose modification or stop of study treatment [3,5,6,7,8] | x[3,6,7,8] | x[3,6,7] | x[3,6,7] | x[3,6,7] | x[3,6,7] | | x[5,6,7] | x[3,6,7] | x[3,6,7] | |
| Evaluation response and protocol failure | x | | | | | | | | | x |
| | | | | | | | | | | |
| **Out site, central laboratory** | | | | | | | | | | |
| GPI-AP-Flow cytometry | x | | | | | | x | | | x |
| Telomeric analysis | x | | | | | | x | | | x |
| Bone marrow preparation [1,2,9] | x | | | | | | | | | x |
| Pharmacokinetic (only in a subgroup of patients) [9] | x[9] | x[9] | x[9] | x[9] | x[9] | | | | | |

### Group B: CR after 6 months Placebo + CSA => end of Placebo, ongoing follow-up

| Visit | Va | VIa | VIIa | VIII | IX |
|---|---|---|---|---|---|
| Weeks after study treatment start (Group B) | 24 | 36 | 48 | 72 | 96 |
| **In site** | | | | | |
| Quality of Life instruments | x | x | x | x | x |
| Physical examination | x | x | x | x | x |
| Anamnesis | x | x | x | x | x |
| Number of transfused units | x | x | x | x | x |
| Bone marrow aspiration and biopsy [1,2] | x | | | | x |
| Cytogenetics | x | | | | x |
| Full blood count with WBC differential | x | x | x | x | x |
| Microscopic peripheral blood count | x | x | x | x | x |
| Reticulocyte count | x | x | x | x | x |
| Ferritin | x | | x | x | x |
| Blood chemistry | x | x | x | x | x |
| ECG | x | | | | x |
| Ophthalmologic examination (cataract) | x | | | | x |
| Evaluation response and protocol failure | x | | x | x | x |
| | | | | | |
| **Out site, central laboratory** | | | | | |
| GPI-AP-Flow cytometry | x | | x | x | x |
| Telomeric analysis | x | | x | x | x |
| Bone marrow preparations [1,2] | x | | | | x |

## Group C: CR or PR after 24 weeks Eltrombopag + CSA => Eltrombopag dose depending on response

| Visit | Va | Vb[9] | Vc | Vd | VIa | VIb | VIIa | VIIb | VIIc | VIII | IX |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Weeks after Eltrombopag-start (Group C) | 24 | 26 | 28 | 32 | 36 | 42 | 48 | 56 | 64 | 72 | 96 |
| **In site** | | | | | | | | | | | |
| Quality of Life instruments | x | x[9] | x | x[9] | x | x | x | x | x | x | x |
| Physical examination | x | x[9] | x | x[9] | x | x | x | x | x | x | x |
| Anamnesis | x | x[9] | x | x[9] | x | x | x | x | x | x | x |
| Number of transfused units | x | x[9] | x | x[9] | x | x | x | x | x | x | x |
| Bone marrow biopsy and aspiration with cytogenetics [1,2,9] | x[2] | | | | | | x | | | | x |
| Cytogenetics | x[2] | | | | | | x | | | | x |
| Full blood count with WBC differential | x | x[9] | x | x[9] | x | x | x | x | x | x | x |
| Microscopic peripheral blood count | x | x[9] | x | x[9] | x | x | x | x | x | x | x |
| Reticulocyte count | x | x[9] | x | x[9] | x | x | x | x | x | x | x |
| Ferritin | x | | | | x | | x | | | x | x |
| Blood chemistry | x | x[9] | x | x[9] | x | x | x | x | x | x | x |
| ECG | x | x[9] | | x[9] | | | x | | | | x |
| Ophthalmologic examination (cataract) | x | | | | | | x | | | | x |
| Drug dispensary/withdrawal | x | | | | x | | x | | | x | |
| Dose modification or stop of study treatment [3,5,6,7,8] | x[3,6,7,8] | x[3,6,7] | x[3,6,7] | x[3,6,7] | x[3,6,7] | x[5,6,7] | x | | | | |
| Evaluation response and protocol failure | x | | | | | | x | | | x | x |
| | | | | | | | | | | | |
| **Out site, central laboratory** | | | | | | | | | | | |
| GPI-AP-Flow cytometry | x | | | | | | x | | | x | x |
| Telomeric analysis | x | | | | | | x | | | x | x |
| Bone marrow preparation [1,2,9] | x | | | | | | x | | | | x |

## Group D: no PR after 24 weeks Eltrombopag + CSA => end of study treatment, ongoing follow-up

| Visit | Va | VIa | VIIa | VIII | IX |
|---|---|---|---|---|---|
| Weeks after Eltrombopag-start (Group D) | 24 | 36 | 48 | 72 | 96 |
| **In site** | | | | | |
| Quality of Life instruments | x | x | x | x | x |
| Physical examination | x | x | x | x | x |
| Anamnesis | x | x | x | x | x |
| Number of transfused units | x | x | x | x | x |
| Bone marrow aspiration and biopsy [1,2] | x | | | | x |
| Cytogenetics | x | | | | x |
| Full blood count with WBC differential | x | x | x | x | x |
| Microscopic peripheral blood count | x | x | x | x | x |
| Reticulocyte count | x | x | x | x | x |
| Ferritin | x | | x | x | x |
| Blood chemistry | x | x | x | x | x |
| ECG | x | | | | x |
| Ophthalmologic examination (cataract) | x | | | | x |
| Evaluation response and protocol failure | x | | x | x | x |
| | | | | | |
| **Out site, central laboratory** | | | | | |
| GPI-AP-Flow cytometry | x | | x | x | x |
| Telomeric analysis | x | | x | x | x |
| Bone marrow preparations [1,2] | x | | | | x |

1 bone marrow examination was performed before start/end of the study treatment, eltrombopag dose escalation or start of eltrombopag in group A
2 bone marrow analysis was performed independent of the study in cases suspicious for progression in SAA/VSAA or a malignant hematologic disorder
3 reduction/stop of eltrombopag if platelets >150 G/l (without thromboembolic history) or >100 G/l (with thromboembolic history) and sufficient erythrocyte + granulocyte response
4 in case of no response stop of eltrombopag treatment without tapering
5 in case of PR 12 months after eltrombopag start tapering of eltrombopag
6 in case of CR after a minimum of 6 months eltrombopag treatment tapering of eltrombopag
7 dose reduction/stop of eltrombopag and CSA was not to be done simultaneously
8 option of dose escalation in patients with PR in group A2 and C after consulting the coordinating investigator
9 only in case of dose escalation

### 9.4.2 Appropriateness of measurements

All parameters evaluated in this study as well as the methods to measure them, are standard variables / methods in clinical practice. They are widely used and generally recognized as reliable, accurate and relevant.

### 9.4.3 Primary endpoint

The primary endpoint of the study was the hematologic response rate (CR + PR) at 6 months.

### 9.4.4 Secondary endpoints

The secondary endpoints were:

- Trilineage hematological response rate (CR and PR) at 3, 6, 12 and 18 months
- Single lineage response at 3, 6, 12 and 18 months
- Cumulative incidence of response
- Time to best hematological and single lineage response
- Proportion of patients with need for transfusions and number of units transfused (PRBC and platelet concentrates) since therapy start
- Cumulative incidence of progress to SAA/VSAA or intensive immunosuppressive treatment with ATG
- Toxicity profile as measured using the CTCAE criteria for patients receiving placebo in comparison to patients receiving eltrombopag, both on top of background treatment with CSA
- Relapse rate at 6, 12 and 18 months
- Cumulative incidence of relapse (from best hematological response)
- OS
- FFS
- Telomere lengths and presence of telomerase mutations as biomarkers for response
- QoL as assessed by QoL instruments (FACIT-F SCALE and EORTC QLQ-C30, in Germany in addition with the QoL questionnaire for Non-malignant hematologic disease (QLQ-AA/PNH))

### 9.4.5 Exploratory endpoints

Pharmacokinetic studies for assessment of dose dependency regarding efficiency and safety in a subgroup of patients (not evaluated, see Section 9.4.10).

### 9.4.6 General study assessments

All screening evaluations were completed, and subject eligibility confirmed before initiating treatment. In the event that a visit could not be scheduled at the exact visit day, a window of plus/minus three days was acceptable for the first visit after treatment start (two weeks after treatment start); a window of plus/minus five days was acceptable for monthly visits and a plus/minus of seven days was acceptable for visits less frequently than every month.

Procedures conducted as part of the subject routine clinical management and obtained prior to signing of informed consent might have been utilized for screening or baseline purposes, provided the procedure met the protocol defined criteria and was performed within 28 days

prior to baseline.

General procedures:

- Information about study procedures and purpose
- Signed informed consent
- Information to female patients of childbearing potential to take oral contraceptives or use a barrier method of birth control to refrain from pregnancy at least for 28 days after last dose of study drug and that they had to inform the local investigator immediately if they got pregnant during the study
- Enrollment by study enrollment / randomization form in case the eligibility criteria were met
- eCRF documentation and maintenance of the ISF
- Drug dispensary

Safety and efficacy assessment before start and during therapy:

- Collection of demographic data and medical history, especially transfusion history (including the dates of transfusions, number of units, blood counts prior and post transfusion)
- Complete physical examination
- Full blood count with WBC differential and microscopic peripheral blood count
- Reticulocyte count
- Blood samples for blood chemistry and coagulation profile: creatinine, urea, uric acid, glucose, LDH, AST, ALT, GGT, AP, protein, bilirubin (direct and total), INR, PTT, CSA trough level
- Bone marrow histology and cytology (in case of suspicious changes in blood count earlier than suggested in the table of study assessments)
- Cytogenetics
- QoL instruments (FACIT-F SCALE / EORTC QLQ-C30, in Germany and some other countries in addition with the QLQ-AA/PNH)
- Ophthalmologic examination (cataract)
- ECG, QT-time
- In female patients of childbearing potential, a pregnancy test was performed with a negative result before inclusion in the study
- Pregnancy test might have been repeated at each visit at the discretion of the investigator
- Pregnancy test was repeated at each visit for all women of childbearing potential in France

Samples were collected and sent to a central lab for telomere length assessment and mutational analysis of telomerase and shelterin complex, GPI-AP flow cytometry and bone marrow morphology review (only in selected cases).

### 9.4.7 Bone marrow examinations

A baseline bone marrow examination including cytomorphology, histopathology and cytogenetics was completed for the study. In case the patient was not willing to undergo the procedure again, bone marrow examinations up to 12 weeks prior to randomization were acceptable, provided the clinical course of disease had not worsened since the bone marrow examination was performed and all required information was available, including platelet count, hemoglobin, neutrophils, WBC and cytogenetic analysis. The diagnosis of MDS was to be excluded for sure by the available bone marrow analysis.

A subsequent bone marrow examination was done at the end of the study treatment phase. In addition, a bone marrow analysis was performed within 14 weeks before start of eltrombopag in group A (placebo group) and eltrombopag dose escalation. Eltrombopag was started or escalated in cases without signs of dysplasia or progression to SAA or VSAA

An unscheduled bone marrow examination was considered for subjects who showed disease progression or unexplained changes in blood count. In these cases, additional samples and slides were requested by the central laboratory in Ulm, Germany.

Differentiation between MAA and hypoplastic MDS can be very difficult. Therefore, a central morphology review was conducted for unclear cases or progress to MDS or AML. For that purpose, morphology slides of all bone marrow examinations within the study were to be collected in the central laboratory in Ulm, Germany. Treatment decisions were based on local laboratory assessment of bone marrow examinations.

### 9.4.8 Assessment of efficacy

#### 9.4.8.1 Hematologic response

The primary endpoint of the study was the hematologic response (CR + PR) at 6 months. Hematological response was demonstrated by a minimum of 3 determinations over a period of at least 2 weeks, starting at least 2 weeks after last transfusion. The first time patients achieved response was considered as the time point. The investigator classified hematological response into complete, partial and no response:

**Complete response (CR) was defined according to Marsh et al [1] as:**

- ANC > 2.0 G/L
- Platelet count > 100 G/L
- and transfusion independence

**Partial response (PR) was defined according to Marsh et al [1] as:**

- ANC > 1.0 G/L
- Platelet count > 30 G/L
- and transfusion independence

Transfusion independence was defined as

- no need for prophylactic platelet transfusions (platelet counts < 10 G/L without bleeding) in the last 4 weeks prior to evaluation
- no need for therapeutic platelet transfusion because of bleeding (not explained by an adequate trauma) in the last 4 weeks prior to evaluation
- no need for packed red blood cell concentrates (pRBC) in the last 6 weeks prior to evaluation

Patients who remained transfusion-dependent were classified as non-responders regardless of the ANC and platelet count.

#### 9.4.8.2 Single lineage response

A secondary endpoint was the potential single lineage response as defined by changes in the platelet count, and/or platelet transfusion requirements, hemoglobin levels, number of red

blood cell transfusions or ANC counts as measured by International Working Group criteria.

**Platelet response** was defined as:

- patients without platelet transfusion dependence: platelet count raised by 20 G/L above baseline
- patients with transfusion dependence for platelets at start of treatment: stable or increasing platelet counts with transfusion independence for a minimum of 8 weeks

**Erythroid response** for subjects with pre-treatment hemoglobin of less than 9 g/dL was defined as:

- an increase in hemoglobin by > 1.5 g/dL
- or an increase of the reticulocyte count 20 G/L above baseline or a reduction in the units of pRBC transfusions by an absolute number of at least 4 pRBC transfusions for 8 consecutive weeks compared with the pre-treatment transfusion number in the 8 weeks previous study entry

**Neutrophil response** was defined as:

- an absolute increase in ANC of > 0.5 G/L
- at least a 100% increase over the baseline ANC in those with pre-treatment absolute ANC of ≤ 0.5 G/L

#### 9.4.8.3 Relapse

Relapse rates were only calculated for patients with at least one single or trilineage response.

Relapse was specified as one of the following events:

- Platelet count < 70 G/L and ANC < 1.2 G/L (criteria for MAA)
- Either platelet count < 70 G/L or ANC < 1.2 G/L and reticulocytes < 60 G/L (criteria for MAA)
- Any platelet transfusion within the last 4 weeks before evaluation (as evaluated by the investigator and documented at time of next visit)
- Any pRBC transfusion within the last 6 weeks before evaluation (as evaluated by the investigator and documented at time of next visit)
- Platelet count below baseline platelet count in case of platelet response
- Neutrophil count below baseline neutrophil count in case of neutrophil response
- Hemoglobin (HgB) value below baseline HgB value in case of erythroid response

Additionally, a post-hoc analysis with modified relapse criteria was performed. For the post hoc analysis, relapse from **first** trilineage response was defined as no longer meeting criteria for at least PR (i.e. patients must have received at least PR – and the next assessment which did no longer fulfill criteria for at least PR was considered as relapse (modified criteria) and the visit date was the date of relapse).

According to the CSP, peripheral blood count decrease was to be demonstrated for a minimum of two times over a period of 2 weeks to qualify as a relapse. However, since second measurements were not documented in the eCRF, calculation of relapse referred only to one measurement.

#### 9.4.8.4 Failure-free survival (FFS)

FFS was defined as survival with trilineage hematological response, i.e. time to treatment failure was calculated as date of death from any cause or date of visit Va (in case of non-response at Va) or date of last treatment (in case of missing date of Va) or date of relapse or date of documented disease progression to MDS or AML or start date of IST or stem cell transplantation whichever occurred first – date of therapy start.

#### 9.4.8.5 QoL and clinical symptoms

QoL was assessed with the QoL questionnaires of the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) and the organization for Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue SCALE) at the start of study treatment and every month during the study treatment phase. In addition, a recently designed specific QoL questionnaire for patients with AA and/or PNH (QLQ-AA/PNH) was performed in some of the centers.

Development of clinical signs was evaluated by a specific clinical sign questionnaire provided to the treating physicians asking for the number and kind of bleedings, infections and transfusions as well as anemia symptoms in the last 1 month and 3 months before start of study treatment and at every visit during the study treatment phase.

#### 9.4.8.6 Biomarkers section

In a first step, descriptive statistics to describe the basic features of the biomarker data (GPI-AP flow cytometry, telomere length assessment, mutational analysis of telomerase and shelterin complex) was performed. In a second step, GPI-deficiency, telomere length and presence of telomerase and/or shelterin mutations were analyzed and correlated and tested for significance in regards to response in all patients and in the groups with placebo or eltrombopag treatment.

### 9.4.9 Assessment of safety

Safety endpoints included incidences of bleeding; assessment of severity of AEs regarding WHO grading, especially changes in liver function, bone marrow fibrosis, development of MDS.

Suspected AEs of eltrombopag are the risk of development of hepatotoxicity, thrombotic/thromboembolic complications, cataract, bleeding after discontinuation of eltrombopag, bone marrow reticulin formation and risk of bone marrow fibrosis, malignancies and progression of malignancies (for further details see Section 9.4.9.8).

Suspected AEs due to AA are cytopenias with clinical symptoms like bleedings, infections and anemia as well as clonal evolution (like PNH as well as MDS or AML).

Suspected AEs due to the standard immunosuppressive treatment with CSA are the risk of development of renal dysfunction, hypertension, hepatoxicity, neurotoxicity (especially tremor), skin abnormalities like hirsutism and gum hyperplasia, malignancies, infections, hypomagnesemia and hyperkalemia (for further details see Section 9.4.9.9). Laboratory findings, increases in uric acid and dose-related hyperbilirubinemia were observed in the absence of hepatocellular damage, modest increase of serum triglycerides or cholesterol.

All AEs were graded according to Common Terminology Criteria for Adverse Events v4.0

(CTCAE).

#### 9.4.9.1 Definitions and terminology

**Adverse event (AE)**

An AE was defined as any untoward medical occurrence or effect in a patient treated on a study protocol, which did not necessarily have a causal relationship with the IMP. An AE was therefore described as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the IMP, whether related to the IMP or not.

**Adverse drug reaction (ADR)**

ADRs were defined as all untoward and unintended responses to an IMP related to any dose administered. A causal relationship between the IMP and an AE was at least a reasonable possibility, i.e. the relationship could not be ruled out.

**Serious adverse event (SAE)**

An SAE was defined as any untoward medical occurrence or effect in a patient treated on a study protocol which did not necessarily have a causal relationship with the IMP, that also, at any dose:

- resulted in death
- was life-threatening

  *NOTE: The term "life-threatening" in the definition of "serious" referred to an event in which the patient was at risk of death at the time of the event; it did not refer to an event which hypothetically might have caused death if it were more severe.*

- resulted in persistent or significant disability/incapacity
- required in-patient hospitalization or prolongation of existing hospitalization
- was a congenital anomaly or birth defect or
- was otherwise medically significant (i.e. withdrawal reactions, all accidental or intentional overdoses whether they resulted in an AE or not, or any event which the investigator considered significant, but which was not covered by the above)
- Specific within this study: Increase of ALT > 3.0 x ULN in patients with normal liver function, in patients with increased ALT before start, an increase of ALT ≥ 3.0 x of the start value/alternatively > 5 x ULN (the lower value was to be chosen) combined with:
    - an elevation of bilirubin > 2.0 x ULN (without an accompanying disorder of the biliary tract
    - or elevation of AP > 2 x ULN (Hy's Law)
    - or clinical symptoms indicating liver injury or hepatic decompensation
    - or persistence for 4 weeks
    - thrombotic/thromboembolic complications
    - clonal evolution

**Suspected unexpected serious adverse reactions (SUSAR)**

A SUSAR was defined as an adverse reaction, the nature of severity of which was not consistent with the known IMP information.

A serious event or reaction was not defined as SUSAR when:

- it was serious but expected
- it did not fit the definition of an SAE, whether expected or not.

#### 9.4.9.2 Procedures for AE reporting

All AEs that occurred between the first study-related procedure (i.e. screening) and 30 days post the last study treatment (or after this date if the investigator felt the event was related to the IMP) were recorded. Those meeting the definition of an SAE were reported using the Serious Adverse Event Report form.

Investigators recorded in the eCRF and the patient notes their opinion concerning details of nature, onset, duration, severity and any relationship to IMP.

**Adverse Event – reported term**

An AE term was provided for each AE using the short name as listed in CTCAE v 4.0.

**Adverse Event – severity**

The severity of each AE including any lab abnormality was determined by using CTCAE v4.0 as a guideline, wherever possible. In those cases where the CTCAE criteria did not apply, severity was defined according to the following criteria:

- Mild: Awareness of sign or symptom, but easily tolerated
- Moderate: Discomfort enough to cause interference with normal daily activities
- Severe: Inability to perform normal daily activities
- Life threatening: Immediate risk of death from the reaction as it occurred.

**Adverse Event – causality and relationship**

Causality and relationship to IMP administration were determined as follows:

- None: No relationship between the experience and the administration of the IMP; related to other etiologies such as concomitant medications or patient's clinical state
- Unlikely: The current state of knowledge indicated that the relationship was unlikely
- Possible: A reaction that followed a plausible temporal sequence from administration of the IMP and followed a known response pattern to the suspected IMP. The reaction might also have been produced by the patient's clinical state or other modes of therapy administered to the patient.
- Probable: A reaction that followed a plausible temporal sequence from administration of the IMP and followed a known response pattern to the suspected IMP. The reaction could not be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient.
- Definitely: An AE, which was listed as possible ADR and could not be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s)

**Adverse Event – expectedness**

An expectedness assessment was conducted for all SAEs and recorded appropriately on the SAE Report form. Expectedness of the event to the IMP was determined as follows:

- Expected: The event was listed in the Reference Safety Information (RSI) as expected.
- Unexpected: The event was not listed in the RSI or the severity of the event was greater

than that listed in the RSI (e.g. mild nausea was listed as expected in the SmPC/IB/study protocol but the event was moderate or severe nausea).

#### 9.4.9.3 Reporting and management of SAEs

The Sponsor was responsible for the implementation of appropriate procedures for reporting SAEs as necessary to the responsible competent authorities, ethics committees and principal investigators.

All investigators were thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, was summarized in the ISF and was updated as needed. All SAEs occurring during the observation period were immediately (within 24 hours of the investigator's awareness) reported to the recipient detailed in the manual. All SAEs regardless of relationship to IMP were collected from the first dose of IMP to the last dose of IMP (minimum of 6 months or until the end of the follow-up period whichever was longer). All SAEs regardless of causality to the IMP were collected until the end of the follow-up period.

From the time a subject consented to participate in and completed the study, all SAEs assessed as related to IMP (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to non-IMP (concomitant or rescue/escape medication used for preventive, diagnostic or therapeutic reasons and/or medication given to ensure that adequate medical care was provided for the subject during a trial) were reported promptly to the trial office.

Any SAE brought to the investigator's attention after the subject had completed the study and considered by the investigator as possibly related to IMP was to be reported to the trial office.

In general, the following attributes were assigned when reporting:

- Detailed description of the event
- AE term
- Date of onset and date of resolution
- Severity of the event
- Assessment of relatedness to IMP and action taken
- Assessment of expectedness for the protocol treatment
- Other suspect drugs/devices
- Outcome

All SAEs were followed up until resolution. The investigator was asked to provide interim and follow-up reports, as necessary, if the SAE had not resolved at the time of the initial report. All deaths occurring on study were reported as an SAE and on the eCRFs to the trial office. For all deaths, available autopsy reports should have been sent with the notification.

The clinical trial office reported any SAEs as necessary to the responsible competent authorities, ethics committees, PIs and Novartis.

#### 9.4.9.4 Reporting of clinical safety data to Novartis

The clinical trial office forwarded all SAEs which occurred during the study in patients who were exposed to the study drug with copies of eCRF to Novartis independent of the assessment regarding a potential causality with the study drug by the investigator.

Related data which were unblinded during the study were to be reported within 24 hours after the Sponsor being notified. Related data which were blinded during the study were to be reported within 5 working days after the Sponsor being notified in context of unblinding the study.

The Sponsor had to report information regarding a pregnancy of a study participant or a partner of a study participant after they had been exposed to the study drug during the study within two weeks after being notified, with copies of the eCRF to Novartis. The patient had to be followed to evaluate the outcome of the pregnancy, including an induced abortion, for a minimum of 6–8 weeks after the end of pregnancy.

#### 9.4.9.5 Expedited reporting to competent authorities

As of May 1st 2004, the Sponsors of clinical trials conducted in the EU and EEA must ensure that all relevant information regarding SUSARs are recorded and reported in an expedited fashion.

It is a legal requirement of the Sponsor to report fatal or life-threatening SUSARs within 7 calendar days to the relevant regulatory authorities after receiving first notification of the event. Non-fatal and non-life-threatening SUSARs were to be reported to the regulatory authorities within 15 calendar days.

#### 9.4.9.6 Expedited reporting to ethics committees

The CRO clinical trial office had the responsibility for reporting SUSARs to ethics committees.

#### 9.4.9.7 Informing investigators of safety issues

The CRO clinical trial office had the responsibility for reporting SUSARs to country PIs.

#### 9.4.9.8 Possible side effects of eltrombopag

**Risk of hepatotoxicity**

Eltrombopag administration can cause abnormal liver function. In clinical studies with eltrombopag, increases in serum ALT, AST and bilirubin were observed. These findings were mostly mild (Grade 1–2), reversible and not accompanied by clinically significant symptoms that would indicate an impaired liver function.

Serum ALT, AST and bilirubin were measured prior to and two weeks after initiation of eltrombopag, followed by monthly controls during the dose adjustment phase.

Abnormal serum liver tests were evaluated with repeat testing within 3 to 5 days. If the abnormalities were confirmed, serum liver tests should have been monitored until the abnormalities resolved, stabilized, or returned to baseline levels.

Eltrombopag should have been discontinued or reduced if necessary.

Eltrombopag should not have been used in patients with hepatic impairment (i.e. mild, moderate or severe hepatic impairment (Child-Pugh score > 5) unless the expected benefit outweighed the identified risk. Caution should have been exercised when administering eltrombopag to patients with hepatic disease.

The influence of hepatic impairment on the pharmacokinetics of eltrombopag following

repeated administration was evaluated using a population pharmacokinetic analysis in 28 healthy adults and 79 patients with chronic liver disease (37 mild hepatic impairment, 40 with moderate hepatic impairment, and 2 with severe hepatic impairment). Based on estimates from the population pharmacokinetic analysis, patients with hepatic impairment had higher plasma eltrombopag area under the curve (AUC) values as compared to healthy volunteers, and AUC increased with increasing Child-Pugh score. Compared to healthy volunteers, patients with mild hepatic impairment had approximately 87% to 110% higher plasma eltrombopag AUC values and patients with moderate hepatic impairment had approximately 141% to 240% higher plasma eltrombopag AUC values.

**Thrombotic / thromboembolic complications**

Platelet counts above the normal range present a theoretical risk of thrombotic / thromboembolic complications. In eltrombopag clinical trials for treatment of patients with ITP thromboembolic events were observed at low and normal platelet counts.

Caution should have been used when administering eltrombopag to patients with known risk factors for thromboembolism including but not limited to inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome, PNH), advanced age, patients with prolonged periods of immobilization, malignancies, contraceptives and hormone replacement therapy, surgery / trauma, obesity and smoking.

Platelet counts should have been closely monitored and consideration given to reduce the dose or discontinuing eltrombopag treatment if the platelet count exceeded the target levels. The risk-benefit balance should have been considered in patients at risk of thromboembolic events of any etiology.

**Bleeding following discontinuation of eltrombopag**

Thrombocytopenia was likely to reoccur upon discontinuation of treatment with eltrombopag. Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of ITP patients, which increases the bleeding risk and, in some cases, might have led to bleeding. This risk was increased if eltrombopag treatment was discontinued in the presence of anticoagulants or anti-platelet agents. Additional medical management might have included cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support. Platelet counts should have been monitored weekly for 4 weeks following discontinuation of eltrombopag.

**Bone marrow reticulin formation and risk of bone marrow fibrosis**

Eltrombopag may increase the risk for development or progression of reticulin fibers within the bone marrow. The relevance of this finding, as with other TPO-R agonists, has not been established yet.

Prior to initiation of eltrombopag, the peripheral blood smear and bone marrow should have been examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, CBC with WBC differential should have been performed regularly. If immature or dysplastic cells were observed, peripheral blood smears should have been examined for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient developed new or worsening morphological abnormalities or cytopenia(s), treatment with eltrombopag should have been discontinued and a bone marrow biopsy considered,

including staining for fibrosis.

**Malignancies and progression of malignancies**

TPO-R agonists are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO-R is predominantly expressed on the surface of cells of the myeloid lineage. For TPO-R agonists there is a theoretical concern that they may stimulate the progression of existing hematopoietic malignancies such as MDS.

**Cataracts**

Cataracts were observed in toxicology studies of eltrombopag in rodents. The clinical relevance of this finding is unknown. Monitoring of patients for cataracts was recommended.

### 9.4.9.9 Possible side effects of CSA

The principal adverse reactions of CSA therapy are renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia. The side effects are dose dependent.

Patients who might have been at increased risk such as those with abnormal renal function, uncontrolled infection, hypertension or malignancies, should not receive CSA.

**Nephrotoxicity**

CSA can cause nephrotoxicity. The risk increases with increasing doses of CSA. Renal dysfunction including structural kidney damage is a potential consequence of CSA treatment. Therefore, renal function was monitored during therapy. Care was taken in using CSA with nephrotoxic drugs. Elderly patients should have been monitored with particular care, since decreases in renal function also occur with age. If patients are not properly monitored and doses are not properly adjusted, CSA therapy can be associated with the occurrence of structural kidney damage and persistent renal dysfunction. Nephrotoxicity associated with CSA had been noted in 25% of cases of renal transplantation, 38% of cases of cardiac transplantation, and 37% of cases of liver transplantation. These elevations were often responsive to CSA dosage reduction. Patients receiving CSA require frequent monitoring of serum creatinine. An increase in serum creatinine and blood urea nitrogen (BUN) may occur during CSA therapy and reflects a reduction in the glomerular filtration rate.

Renal function was to be monitored during therapy. Care should have been taken in using CSA with nephrotoxic drugs and in elderly patients.

**Hypertension**

CSA can cause hypertension and the risk increases with increasing dose and duration of therapy. Hypertension, which is usually mild to moderate, may occur in approximately 50% of patients following renal transplantation and in most cardiac transplant patients. Blood pressure has to be monitored closely. Appropriate measures have to be taken if necessary.

**Skin**

Skin abnormalities are a common event during CSA treatment. Hirsutism is observed in 21 - 45% of the transplanted (kidney, heart, liver) patients with CSA treatment. Acne was observed in 1 - 6% of the patients.

An important issue is gum hyperplasia in 4 - 16% of the transplanted (kidney, heart, liver) patients with CSA treatment. This is especially relevant as these patients are on risk for

bleedings and infections in context of the gum hyperplasia.

**Hypomagnesemia**

Mild hypomagnesemia is often seen, sometimes in combination with muscle cramps and pain. Hypomagnesemia has been reported in some, but not all, patients exhibiting convulsions while on CSA therapy. Although magnesium depletion studies in normal subjects suggest that hypomagnesemia is associated with neurologic disorders, multiple factors, including hypertension, high dose methylprednisolone, hypocholesterolemia, and nephrotoxicity associated with high plasma concentrations of CSA appear to be related to the neurological manifestations of CSA toxicity.

**Hyperkalemia**

Significant hyperkalemia (sometimes associated with hyperchloremic metabolic acidosis) and hyperuricemia have been seen occasionally in individual patients.

**Hepatotoxicity**

Cases of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis, and liver failure have been reported in patients treated with CSA. Most reports included patients with significant comorbidities, underlying conditions and other confounding factors including infectious complications and co-medication with hepatotoxic potential. In some cases, mainly in transplant patients, fatal outcomes have been reported**.** Hepatotoxicity, usually manifested by elevations in hepatic enzymes and bilirubin, was reported in patients treated with CSA in clinical trials: 4% in renal transplantation, 7% in cardiac transplantation, and 4% in liver transplantation. This was usually noted during the first month of therapy when high doses of CSA were used. The chemistry elevations usually decreased with a reduction in dosage.

**Malignancies**

As in patients receiving other immunosuppressants, those patients receiving CSA are at increased risk for development of lymphomas and other malignancies, particularly those of the skin. Patients taking CSA should have been warned to avoid excess ultraviolet light exposure. The increased risk appears related to the intensity and duration of immunosuppression rather than to the use of specific agents. Because of the danger of over suppression of the immune system resulting in increased risk of infection or malignancy, a treatment regimen containing multiple immunosuppressants should have been used with caution. Some malignancies may be fatal. Patients should be thoroughly evaluated before and during CSA treatment for the development of malignancies. Tumors were reported in 32 (2.2%) of 1439 psoriasis patients treated with CSA worldwide from clinical trials. Additional tumors have been reported in 7 patients in CSA post marketing experience. Skin malignancies were reported in 16 (1.1%) of these patients; all but 2 of them had previously received PUVA therapy. Methotrexate was received by 7 patients. UVB and coal tar had been used by 2 and 3 patients, respectively. Seven patients had either a history of previous skin cancer or a potentially predisposing lesion was present prior to CSA exposure. Of the 16 patients with skin cancer, 11 patients had 18 squamous cell carcinomas and 7 patients had 10 basal cell carcinomas. There were two lymphoproliferative malignancies; one case of non-Hodgkin's lymphoma which required chemotherapy, and one case of mycosis fungoides which regressed spontaneously upon discontinuation of CSA. There were four cases of benign lymphocytic infiltration: 3 regressed spontaneously upon discontinuation of CSA, while the fourth regressed despite continuation of the drug. The remainder of the malignancies, 13 cases (0.9%), involved various organs.

Therefore, patients should not have been treated concurrently with CSA and PUVA or UVB, other radiation therapy, or other immunosuppressive agents, because of the possibility of excessive immunosuppression and the subsequent risk of malignancies.

Special care was to be taken in patients with psoriasis due to their increased risk for skin cancer.

**Serious infections**

Patients receiving immunosuppressants, including CSA, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Patients receiving immunosuppressants, including CSA, are at increased risk for opportunistic infections, including polyomavirus infections. Both generalized and localized infections can occur. Pre-existing infections may also be aggravated.

Polyoma virus infections in transplant patients may have serious, and sometimes, fatal outcomes. These include cases of JC virus-associated progressive multifocal leukoencephalopathy (PML), and polyoma virus-associated nephropathy (PVAN), especially due to BK virus infection, which have been observed in patients receiving CSA after transplantation. Cases of PML have been reported in patients treated with CSA. PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

**Neurotoxicity**

Tremor was observed in patients after transplantation (kidney, liver, heart) in 12 - 55% of the cases.

Cases of migraine have been reported. In some cases, patients have been unable to continue CSA, however, the final decision on treatment discontinuation should be made by the treating physician following the careful assessment of benefits versus risks.

There have been reports of convulsions in 3 - 5% adult and pediatric patients receiving CSA after transplantation (kidney, liver, heart), particularly in combination with high dose methylprednisolone. Encephalopathy has been described both in post-marketing reports and in the literature. Manifestations include impaired consciousness, convulsions, visual disturbances (including blindness), loss of motor function, movement disorders and psychiatric disturbances. Changes in the white matter have been detected using imaging techniques and pathologic specimens. Predisposing factors such as hypertension, hypomagnesemia, hypocholesterolemia, high-dose corticosteroids, high CSA blood concentrations, and graft-versus-host disease have been noted in many but not all of the reported cases. The changes in most cases have been reversible upon discontinuation of CSA, and in some cases, improvement was noted after reduction of dose. It appears that patients receiving liver transplant are more susceptible to encephalopathy than those receiving kidney transplant. Another rare manifestation of CSA-induced neurotoxicity, occurring in transplanted patients more frequently than in other indications, is optic disc edema including papilloedema, with possible visual impairment, secondary to benign intracranial hypertension.

**Abnormal laboratory findings**

Mild hypomagnesemia and hyperkalemia may occur but are mostly asymptomatic. Increases in uric acid may occur and attacks of gout have been rarely reported. Minor and dose related hyperbilirubinemia has been observed in the absence of hepatocellular damage. CSA therapy may be associated with a modest increase of serum triglycerides or cholesterol. Generally, these laboratory abnormalities are reversible upon dose reduction or discontinuation of CSA.

### 9.4.10 Drug concentration measurements

An additional eltrombopag pharmacokinetic study (PK) was planned in patients with dose escalation of eltrombopag (225 mg eltrombopag daily). Unfortunately, sample collection was not realized in the rare cases with escalated dosage.

## 9.5 Data processing and quality assurance

Responsible for data processing and quality assurance was the Sponsor of the study (for further details see Table 10).

### 9.5.1 Documentation

The IT infrastructure and data management staff was supplied by the CRO, see Table 10. The data management system was based on a commercial trial software and stored the data in a database, storing all changes in an audit trail. Specifications and detailed information were described in the data management plan. The trial software had a user and role concept that could be adjusted on a trial-specific basis. The database was integrated into a general IT infrastructure and safety concept with a firewall and backup system. After completion and cleaning of data, the database was locked and the data exported for statistical analysis.

Trial sites entered the data online via Internet. Plausibility checks were run during data entry, thereby detecting discrepancies immediately. The CRO Data Management conducted further checks for completeness and plausibility and clarified any questions with the trial sites electronically via trial software. Discrepancies and implausible values were clarified in writing between the data manager and the trial site. Further details were specified in the data management manual.

On-site monitoring and monitoring of the trial data as well as data evaluation and statistical analysis were done by the CRO. Medical assessment and interpretation of the data were done by the coordinating investigators and the protocol committee.

### 9.5.2 Monitoring

The study sites were monitored to ensure the quality of the data collected. The objectives of the monitoring procedures were to ensure that the trial subject´s safety and rights as a study participant were respected, that accurate, valid and complete data were collected, and that the trial was conducted in accordance with the trial protocol, the principles of GCP and local legislation.

All investigators agreed that the monitor regularly visit each trial site and ensured that the monitor received appropriate support in his/her activities at the trial site, as agreed in separate contracts with each site. The declaration of informed consent included a statement to the effect that the monitor had the right – while observing the provisions of data protection legislation –

to compare the CRFs with the trial subject's medical records (physician notes, laboratory printouts etc.). The investigator ensured access for the monitor to all necessary documentation for trial-related monitoring. The purposes of the monitor visits were as follows:

- Verify for each new subject that informed consent was obtained prior to the subject´s participation in the study and if necessary, the informed consent of protocol amendments
- Verify if study was conducted in compliance with the CSP and its amendments
- Source Document verification was carried out as specified below:
    - Verify 100% inclusion and exclusion criteria
    - Verify 100% of eCRF data against clinic source data for primary efficacy and safety endpoints
    - Verify at least 50% of eCRF data against clinic source data for secondary efficacy endpoints
    - Verify 100% of SAEs and 25% of AEs were appropriately recorded and that the process of reporting SAEs was followed
    - Verify 100% of drug accountability
- Verify that study drug was adequately stored and that adequate documentation was on file regarding receipt, dispensing and destruction
- Check on expiry date of the study drug
- Monitoring at each investigator trial site was done for the ISF
- Verify that laboratory normal ranges and laboratory certificates were current and still valid
- Ensure that the investigational staff had documented roles and responsibilities, documentation of qualification was present and that new members were trained in trial specific procedures
- Document all activities and discussions with investigational staff in a written report and sent this to the Clinical Trials Office
- Arrange for appropriate follow-up of all action items in the monitoring report

The investigator was obliged to provide source documentation, eCRFs of subjects and the trial related documents to the monitor during all monitoring visits. Investigators should have had ample time to discuss problems and make corrections identified by the monitor.

Further details were given in the Monitoring Manual. A monitoring visit report was prepared for each visit describing the progress of the clinical study and any issues.

### 9.5.3 Audits/Inspections

No audit or inspection was performed during the conduct of this study.

### 9.5.4 Archiving

It is the responsibility of the PI at the study center to keep all essential documents relating to the trial for at least 15 years after the completion or premature termination of the clinical trial. Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the institution complied with the principles and guidelines of GCP.

The medical files of patients enrolled into the trial must be kept in accordance with national legislation and for the maximum period of time permitted by the institution but at least 15 years.

The Sponsor or subsequent owner is required to keep all other documentation for the life of the product studied. The archived data can be kept in electronic form, provided that a back-up copy is kept and that a paper copy can be provided if necessary. The protocol, ethical and government approvals, together with all other documents concerning the study, including any audit and inspection certificates are all to be kept as part of the TMF. All data about SAEs also need to be kept in this TMF.

All data should be available for inspection by the appropriate authorities on demand.

## 9.6 Statistical hypothesis and sample size calculation

All statistical analyses were pre-specified in the CSP (version 6.0, dated 09 Oct 2024) and in the SAP (version 1.0, dated 08 Jan 2025).

The statistical evaluation was performed by using the software package R Version 4.4.1 (GNU General Public License, www.r-project.org).

Documentation of the statistical methodologies used can be found in Section 16.1.9.

### 9.6.1 Analysis datasets

**Full analysis set (FAS)**

The primary analysis set was the FAS. The FAS consisted of all patients randomized. All efficacy analyses were based on the FAS. Comparisons between groups were performed using the arm assigned at randomization.

In the case of patients found to be not eligible after randomization or going off-study before receiving the treatment, these cases were excluded, and secondary analyses were performed to check the sensitivity of conclusions when these cases were included.

**Per protocol set (PPS)**

The PPS included all patients evaluable at 6 months after therapy start. The analysis of the primary endpoint was based on PPS. Patients alive at 6 months and non-evaluable or withdrawals before 6 months were excluded from the primary analysis.

**Safety analysis set (SAF)**

The safety analyses were performed on the SAF, defined as the subpopulation of patients who received at least 10 weeks of study treatment.

### 9.6.2 Sample size calculation

The primary endpoint of the study was the hematologic response (CR + PR) at 6 months.

This was a superiority study aiming to increase the 6-months hematologic response (CR + PR) rate.

Baseline response (PR+CR) expectation after 6 months with standard immunosuppression with CSA alone was 46% [1]. The sample size was calculated on the hypothesis that in the experimental arm the addition of eltrombopag to background treatment with CSA increases the 6-months response rate (CR + PR) up to 71%. In these conditions, for a targeted power of 80% and at a 5% significance level (one-sided test) a number of n = 90 evaluable patients (45 patients in each group, placebo and eltrombopag) was required. After applying a correction for

a loss to follow-up rate of 5%, 94 patients (47 in each group, placebo and eltrombopag) would have to be accrued.

Sample size calculation for a superiority trial (one-sided test) with binary outcome based on the formula:

$n = (Z_\alpha + Z_\beta)^2 \times \{p_1 \times (100-p_1) + p_2 \times (100 - p_2)\} / (p_2-p_1)^2$

$p_1$ and $p_2$ are the percent "success" in the control and experimental group respectively, and $Z_\alpha$ and $Z_\beta$ are the α- and β-quantiles of the standard normal distribution.

Software provided by www.sealedenvelope.com was used for sample size calculation.

### 9.6.3 Randomization / stratification

See Section 9.6.3.

### 9.6.4 Variables and planned statistical analyses

Primary and secondary variables are specified in Sections 9.4.3 and 9.4.4.

### 9.6.5 Statistical methods

A detailed SAP (see Section 16.1.9) was compiled and reviewed prior to the end of the data management process.

### 9.6.6 Subgroup analyses

A subgroup analysis was neither planned nor performed.

### 9.6.7 Interim analysis

An interim analysis was neither planned nor performed.

## 9.7 Closure of study sites / Premature termination of the clinical study

It was planned to terminate the study after completion of the last follow-up (LPLV), i.e. after the last recruited patient had completed 24 months follow-up after the start of study treatment.

Circumstances that might have warranted early termination included, but were not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to recruit patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the study drug

Unexpected, significant, or unacceptable risk to patients included:

- Excess of mortality in the investigational arm (after at least 15 patients enrolled in each arm)
- Excess rate of clonal evolution (after at least in 15 patients of each arm cytogenetics were performed). Clonal evolution was defined as any of the following:
    - diagnosis of acute leukemia
    - diagnosis of MDS, according to established criteria (by morphology, flow cytometry

and karyotype) as defined by WHO 2016 criteria
  - occurrence of any cytogenetic abnormality (excluding PIG-A mutation/PNH) which was demonstrated in at least 10% of bone marrow cells in at least two bone marrow specimens drawn with an interval of at least 3 months.

- Excess of unacceptable morbidity (especially nephrotoxicity and hepatotoxicity) in the investigational arm (after at least 15 patients of each arm at 6 months follow-up)

Investigators could terminate participation in the study. If this occurred, they should have provided a written statement of the reasons for terminating participation and should have provided the trials office with all available and up-to-date study data.

The sponsor could also decide to terminate participation of an investigator or study center for the following reasons:

- Breach of agreement
- Serious non-compliance to GCP standards
- Insufficient patient recruitment

If a participating center closed, or was closed, prior to termination of the whole trial, the Sponsor expected that data from patients already entered into the trial were reported as per protocol.

### 9.8 Changes in the conduct of the study or planned analyses

The study was conducted according to the CSP version 1.15 dated 08 Jan 2015 and the following amendments:

- Version 2.0 dated 08 May 2017: change of financial support and marketing authorization holder of IMP
- Version 3.0 dated 31 May 2017: corrections of terms and clarifications approved by the ethics committee
- Version 4.0 dated 03 Mar 2020: reduction of sample size and follow-up period, modification of the pharmacokinetic section, adjustment of eltrombopag treatment period
- Version 4.1 dated 22 Jul 2021: initial protocol for France
- Version 5.0 dated 28 Apr 2022: extension of recruitment period and adjustment of study timelines, addition of telomeric analysis and flow cytometry for Group A2 visit XIII
- Version 6.0 dated 09 Oct 2024: administrative changes at the Sponsor, addition of an exploratory endpoint, change of the end of trial definition

There were no amendments or supplements to the SAP. Deviations from the SAP are described in Section 16.1.9.

## 10 Study subjects

### 10.1 Disposition of subjects

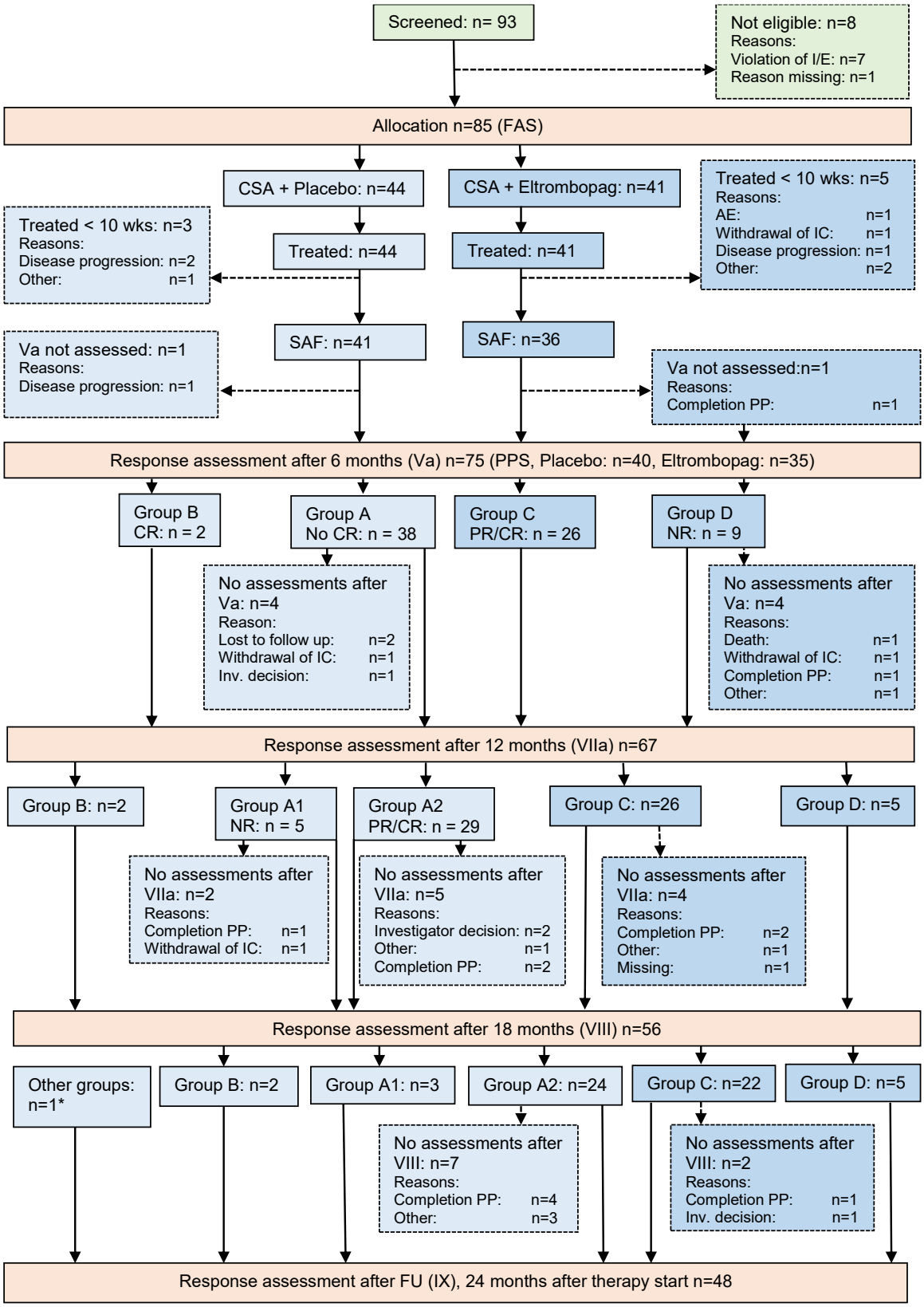
A summary on subject disposition is given in Figure 3. For further information please refer to Section 14.1.1. A listing of patients who did not complete the study per protocol is provided in Table 16.2.1.1. Reasons for discontinuations are listed in Section 14.1.1. Assignment to treatment arms and groups is listed in Section 16.2.3.1.

Clinical conduct of the study was between 27 May 2015 (date of first informed consent) and 23 Dec 2024 (LPLV).

Ninety-three (93) patients were enrolled and screened at nine study centers. Of them, 85 patients successfully completed screening and were randomized to one of the two treatment arms, 44 of them to receive CSA plus placebo and 41 patients to receive CSA plus eltrombopag. Six months after therapy start, treatment was unblinded and patients newly assigned to treatment with CSA plus eltrombopag on the basis of their response assessment. A further decision on treatment with CSA and eltrombopag was based on the 12-month response assessment. More details on subject disposition are given in Figure 3.

One patient was wrongly allocated to Group C after response assessment at 6 months without having achieved trilineage response instead of correct assignment to Group D. Another patient was wrongly allocated to Group A1 after response assessment at 12 months although PR was achieved, instead of correct assignment to Group A2. Both patients were included in the analysis sets with the group to which they were assigned. However, this had no impact on the outcome of the primary endpoint, as the misclassification followed the response assessments at 6 and 12 months, respectively.

**Figure 3: Subject disposition**




*: One patient had only one response assessment which was performed at visit IX.

Source: Section 14.1.1

## 10.2 Protocol deviations

Overall, 23 major protocol deviations were reported including incomplete/inconsistent ICF (n=4), amended ICF version missing (n=1), violation of one or more eligibility criteria (n=2) and protocol violations such as visit outside the specified time window or not performed (n=4), assessments not done (n=2), incorrect IMP treatment or implausible drug account (n=7) and others (n=3). Further, 36 minor protocol deviations were reported which were related to ICF (n=5), eligibility criteria (n=1) and protocol violations such as visit outside the specified time window (n=14), assessments not done (n=6), incorrect IMP treatment or implausible drug account (n=6), source data not verifiable (n=1) and others (n=3). An exhaustive list of protocol deviations can be found in the TMF.

## 10.3 Data sets analyzed

For definition of analysis datasets see Section 9.6.1.

All 85 patients who received at least one dose of study medication were included in the FAS. Seventy-seven patients received treatment for ≥ 10 weeks and were included in the SAF, 41 in the placebo group and 36 in the eltrombopag group. For one of the SAF patients in each treatment arm no response assessment was available at visit Va. Therefore, these patients were excluded from the PPS.

Please refer to Figure 3 and Listing 16.2.3 for further information.

## 10.4 Demographic and other baseline characteristics

A summary of selected demographic and clinical baseline characteristics of the FAS population is shown in Table 12. Summary statistics for demographic data and baseline characteristics are given in Section 14.1.2. Patient listings of demographic data and medical history are provided in Section 16.2.3 and Section 16.2.5, respectively.

**Table 12: Selected demographic and baseline clinical characteristics (FAS)**

| Patient characteristics | | | Eltrombopag N=41 | Placebo N=44 | Total N=85 |
|---|---|---|---|---|---|
| Sex | Male | n (%) | 23 (56.1%) | 22 (50.0%) | 45 (52.9%) |
| | Female | n (%) | 18 (43.9%) | 22 (50.0%) | 40 (47.1%) |
| Ethnicity | Caucasian | n (%) | 35 (85.4%) | 39 (88.6%) | 74 (87.1%) |
| | Asian | n (%) | 2 (4.9%) | 1 (2.3%) | 3 (3.5%) |
| | Other | n (%) | 4 (9.8%) | 4 (9.1%) | 8 (9.4%) |
| Age (years) | | Arithmetic mean / STD | 51.9 / 18.0 | 49.8 / 19.2 | 50.8 / 18.5 |
| | | Median (IQR) | 55.0 (35.0-65.0) | 46.5 (35.5-65.2) | 53.0 (35.0-65.0) |
| | | Range | 20 - 84 | 19 - 83 | 19 - 84 |
| | 18-60 years | n (%) | 25 (61.0%) | 28 (63.6%) | 53 (62.4%) |
| | > 60 years | n (%) | 16 (39.0%) | 16 (36.4%) | 32 (37.6%) |
| Transfusion-dependency | yes | n (%) | 27 (65.9%) | 22 (50.0%) | 49 (57.6%) |
| GPI deficient erythrocytes (%) | | Arithmetic mean / STD | 1.7 / 5.0 | 1.4 / 2.8 | 1.6 / 4.0 |
| | | Median (IQR) | 0.0 (0.0-0.2) | 0.1 (0.0-1.0) | 0.1 (0.0-0.7) |
| | | Range | 0 - 23 | 0 - 10 | 0 - 23 |

| Patient characteristics | | Eltrombopag N=41 | Placebo N=44 | Total N=85 |
|---|---|---|---|---|
| GPI deficient granulocytes* (%) | Arithmetic mean / STD | 7.7 / 16.8 | 9.0 / 16.2 | 8.4 / 16.3 |
| | Median (IQR) | 0.2 (0.0-1.6) | 0.8 (0.1-8.5) | 0.5 (0.0-8.0) |
| | Range | 0 - 65 | 0 – 65 | 0 – 65 |
| Hemoglobin (g/L) | Arithmetic mean / STD | 90.4 / 12.9 | 89.1 / 14.1 | 89.8 / 13.5 |
| | Median (IQR) | 90.0 (85.0 - 98.0) | 93.7 (80.2 – 100.0) | 90.0 (82.1 – 98.0) |
| | Range | 64 – 124 | 65 – 117 | 64 – 124 |
| Reticulocytes (g/L) | Arithmetic mean / STD | 50.1 / 27.5 | 56.0 / 21.8 | 53.2 / 24.7 |
| | Median (IQR) | 41.7 (28.2 - 76.2) | 54.0 (40.8 – 71.2) | 52.8 (34.6 – 76.2) |
| | Range | 5 - 106 | 17 - 101 | 5 - 106 |
| ANC ($10^9$/L) | Arithmetic mean / STD | 1.04 / 0.44 | 1.14 / 0.70 | 1.09 / 0.59 |
| | Median (IQR) | 1.07 (0.64 – 1.29) | 0.90 (0.64 – 1.42) | 0.98 (0.64 – 1.29) |
| | Range | 0.0 – 2.1 | 0.1 – 3.3 | 0.0 – 3.3 |
| Platelet count ($10^9$/L) | Arithmetic mean / STD | 24.5 / 20.2 | 30.0 / 32.7 | 27.4 / 27.4 |
| | Median (IQR) | 20.0 (12.0-27.0) | 23.0 (18.5-33.2) | 22.0 (14.0-29.0) |
| | Range | 4 -116 | 2 - 222 | 2 -222 |
| Number of platelet concentrate transfusions* | Arithmetic mean / STD | 3.7 / 3.3 | 5.1 / 5.9 | 4.4 / 4.6 |
| | Median (IQR) | 2.0 (1.2-5.5) | 3.0 (1.0-7.5) | 2.0 (1.0-6.0) |
| | Range | 1 - 12 | 0 - 22 | 0 - 22 |
| Number of packed red blood cell transfusions* | Arithmetic mean / STD | 4.4 / 4.1 | 4.2 / 2.2 | 4.3 / 3.3 |
| | Median (IQR) | 3.0 (2.0-4.8) | 4.0 (2.0-6.0) | 4.0 (2.0-6.0) |
| | Range | 1 - 18 | 1 - 9 | 1 - 18 |
| Number of transfusions since diagnosis* | Arithmetic mean / STD | 6.4 / 6.4 | 7.4 / 7.0 | 6.9 / 6.6 |
| | Median (IQR) | 4.0 (2.0-7.0) | 5.0 (2.0-10.0) | 4.0 (2.0-8.0) |
| | Range | 1 - 22 | 1 - 28 | 1 - 28 |

*subset of patients transfused
Source: Tables 14.1.2.2 and 14.1.2.3

### Table 13: Baseline medical history and anamnesis (FAS)

| Number of patients n (%) | Eltrombopag N=41 | Placebo N=44 | Total N=85 |
|---|---|---|---|
| **Medical history** | | | |
| Cardiovascular events | 12 (29.3%) | 18 (40.9%) | 30 (35.3%) |
| Neurological disorders / events | 5 (12.2%) | 10 (22.7%) | 15 (17.6%) |
| Endocrine disorders | 9 (22.0%) | 12 (27.3%) | 21 (24.7%) |
| Gastrointestinal and hepato-pancreato-biliary events | 10 (24.4%) | 7 (15.9%) | 17 (20.0%) |
| Persistent or serious infections | 2 (4.9%) | 1 (2.3%) | 3 (3.5%) |
| Hematologic / oncologic disease | 13 (31.7%) | 14 (31.8%) | 27 (31.8%) |
| Musculoskeletal disorders | 9 (22.0%) | 12 (27.3%) | 21 (24.7%) |
| Surgeries | 16 (39.0%) | 18 (40.9%) | 34 (40.0%) |
| Renal and urinary tract events | 4 (9.8%) | 5 (11.4%) | 9 (10.6%) |
| Autoimmune disease | 11 (26.8%) | 11 (25.0%) | 22 (25.9%) |

| Number of patients n (%) | Eltrombopag N=41 | Placebo N=44 | Total N=85 |
|---|---|---|---|
| Pulmonary disease | 5 (12.2%) | 6 (13.6%) | 11 (12.9%) |
| Thromboembolic events | 3 (7.3%) | 5 (11.4%) | 8 (9.4%) |
| Familial history of hematologic / oncological disease | 11 (26.8%) | 8 (18.2%) | 19 (22.4%) |
| **Anamnesis** | | | |
| Anemia signs in the last 12 weeks | 22 (53.7%) | 26 (59.1%) | 48 (56.5%) |
| Bleeding signs in the last 12 weeks | 11 (26.8%) | 19 (43.2%) | 30 (35.3%) |
| Hemolysis signs in the last 12 weeks | 2 (4.9%) | 1 (2.3%) | 3 (3.5%) |
| Infections in the last 12 weeks | 7 (17.1%) | 6 (13.6%) | 13 (15.3%) |
| Concomitant medication | 29 (70.7%) | 35 (79.5%) | 64 (75.3%) |
| Transfusions in the last 12 weeks | 27 (65.9%) | 22 (50.0%) | 49 (57.6%) |

Source: Table 14.1.2.3

### 10.5 Prior and concomitant medication

A patient listing of prior and concomitant medication including dosing details and indication is provided in Section 16.2.6.

## 11 Efficacy evaluation

For study endpoints please refer to Sections 9.4.3 and 9.4.4.

### 11.1 Treatment compliance and duration

For eltrombopag dosing details see Section 9.3.2.1. Data on drug administration and compliance are summarized in Section 14.1.3.

For 76/85 patients of the FAS (89.4%) treatment compliance was demonstrated, for 90.2% of patients in the Eltrombopag Arm and for 88.6% in the Placebo Arm (see Table 14.1.3.6).

Within the first 6 months of treatment, none of the patients in the Eltrombopag Arm required an interruption of eltrombopag while for 5 patients (12.2%) the eltrombopag dose was reduced due to increase in transaminases, CR, dose adjustment per protocol, platelets and elevated thromboembolic event risk at start of eltrombopag therapy. In 4 patients (9.8%) eltrombopag treatment was permanently stopped (2 patients EOS, 1 patient with PD and 1 patient due to development of exanthema), see Table 14.1.3.1. For 5 patients of the Eltrombopag Arm (12.2%), an increase in dose was reported (see Table 14.1.3.3). Reasons for dose adjustments are listed in Table 14.1.3. 3.

For a summary of treatment compliance and duration beyond the first 6 months see Section 14.1.3. Information on total eltrombopag exposure is provided in Table 14.

**Table 14: Summary on eltrombopag exposure (FAS)**

| Parameter | | Eltrombopag N=41 | Placebo* N=44 | Total N=85 |
|---|---|---|---|---|
| Mean daily dose (mg) | N | 32 | 16 | 48 |
| | Arithmetic mean / STD | 103.43 / 51.88 | 112.36 / 68.73 | 106.41 / 57.46 |
| | Median (IQR) | 112.28 (63.35-143.57) | 111.06 (63.63-145.40) | 111.23 (63.58-143.57) |
| | Range | 9.8 – 204.4 | 20.3 – 255.8 | 9.8 – 255.8 |
| Mean daily dose within the first 6 months (mg) | N | 32 | 16 | 48 |
| | Arithmetic mean / STD | 179.81 / 126.31 | 142.24 / 62.46 | 167.29 / 109.95 |
| | Median (IQR) | 153.12 (77.46-291.85) | 150.45 (95.09-171.76) | 150.45 (79.91-228.35) |
| | Range | 12.5 – 434.4 | 40.2 – 262.5 | 12.5 – 434.4 |
| Total dose (mg) | N | 32 | 17 | 49 |
| | Arithmetic mean / STD | 30209 / 21220 | 38338 / 23751 | 33029 / 22229 |
| | Median (IQR) | 25725 (13012-49031) | 32250 (17250-60975) | 27900 (14100-50100) |
| | Range | 2100 - 72975 | 8400 - 86250 | 2100 - 86250 |
| Total dose within the first 6 months (mg) | N | 32 | 16 | 48 |
| | Arithmetic mean / STD | 30209 / 21220 | 23897 / 10494 | 28105 / 18471 |
| | Median (IQR) | 25725 (13012-49031) | 25275 (15975-28856) | 25275 (13425-38363) |
| | Range | 2100 - 72975 | 6750 - 44100 | 2100 – 72975 |
| Total duration of exposure (weeks) | N | 41 | 34 | 75 |
| | Arithmetic mean / STD | 45.47 / 28.60 | 50.28 / 17.47 | 47.65 / 24.17 |
| | Median (IQR) | 47.86 (23.86-68.14) | 49.43 (34.18-61.93) | 48.86 (26.21-63.86) |
| | Range | 0.7 – 126.0 | 23.9 – 78.1 | 0.7 – 126.0 |
| Duration of observation (months) | N | 41 | 44 | 85 |
| | Arithmetic mean / STD | 21.10 / 11.08 | 20.63 / 9.07 | 20.86 / 10.03 |
| | Median (IQR) | 22.47 (13.60-28.42) | 22.08 (15.55-23.38) | 22.08 (14.88-24.80) |
| | Range | 0.2 – 40.9 | 0.5 – 41.3 | 0.2 – 41.3 |

*refers to medication with eltrombopag after end of placebo treatment
Source: Table 14.1.3.7

## 11.2 Efficacy results

### 11.2.1 Analysis of the primary efficacy endpoint

Summary data for the primary endpoint are given in Section 14.2.1. Results from the sensitivity and subgroup analyses of the primary endpoint are shown in Section 14.2.2. Individual patient listings for the primary endpoint can be found in Section 16.2.4.

The primary endpoint of the study was the trilineage hematologic response rate (CR + PR) at 6 months after start of study medication. The analysis of the primary endpoint was based on the PPS.

The response assessment was calculated as defined by the response criteria [1]. Additionally, the investigator classified the hematologic response. Both assessments were evaluated descriptively, but the investigator assessment was used for hypothesis testing.

According to the investigator assessment 25/35 patients (71.4%) showed hematologic response at 6 months after start of treatment with eltrombopag and 17/40 patients (42.5%) had hematologic response in the placebo group. The response rate was significantly higher after treatment with eltrombopag as compared to the placebo group (p=0.011; OR 3.325; LL for OR 1.354), see Table 15.

Older age (above 60 years) did not have a significant impact on the outcome of the primary endpoint, whereas patients with transfusion-dependent MAA had a significantly lower chance of reaching the primary endpoint (p=0.007; OR 0.18; 95% CI [0.05; 0.63]), see Table 16.

**Table 15: Trilineage hematological response at 6 months according to investigator assessment (PPS)**

| Response assessment | Eltrombopag N=35 | | Placebo N=40 | | Comparison of treatment arms | | |
|---|---|---|---|---|---|---|---|
| Response | N | % [95% CI] | N | % [95% CI] | p-value | OR | 95% LL for OR |
| CR | 4 | 11.4 [3.9; 26.5] | 2 | 5 [NA; NA] | | | |
| PR | 21 | 60 [43.5; 74.5] | 15 | 37.5 [24.2; 53] | | | |
| NR | 10 | 28.6 [16.2; 45.2] | 23 | 57.5 [42.2; 71.5] | | | |
| Yes (CR or PR) | 25 | 71.4 [54.8; 83.8] | 17 | 42.5 [28.5; 57.8] | 0.011 | 3.325 | 1.354 |
| No (NR) | 10 | 28.6 [16.2; 45.2] | 23 | 57.5 [42.2; 71.5] | | | |

NA not applicable
Source: Table 14.2.1.1

**Table 16: Trilineage hematological response at 6 months – subgroup analysis (FAS)**

| Factor | OR | p-value | 95% CI |
|---|---|---|---|
| Arm: eltrombopag | 3.49 | 0.015 | [1.27; 9.59] |
| > 60 years old | 1.74 | 0.545 | [0.29; 10.50] |
| Transfusion-dependent MAA | 0.18 | 0.007 | [0.05; 0.63] |
| > 60 years old and transfusion-dependent MAA | 0.52 | 0.566 | [0.06; 4.83] |

Source: Table 14.2.2.4

As indicated in Figure 3, 10 patients from the FAS were not included in the PPS. As defined in the CSP a sensitivity analysis was performed to check the validity of conclusions. The scenarios for non-evaluable patients and withdrawals were: i) all cases failures; ii) all cases CR; iii) all experimental arm cases failures, all control arm cases CR. As shown in Table 17, the different response among groups remained significant in scenario i) and ii). Only in the “worst case scenario” that assumes that all missing patients in the Eltrombopag Arm were failures and all missing patients in the control arm achieved CR, the difference in the response rate (61.0% in eltrombopag vs. 47.7% in the control arm) would no longer reach statistical significance (p=0.157).

**Table 17: Trilineage hematological response at 6 months according to investigator assessment - sensitivity analysis (FAS)**

| Scenario | Response assessment<br>Response | Eltrombopag N=41<br>N (%) | Placebo N=44<br>N (%) | Comparison of treatment arms<br>p-value | OR | 95% LL for OR |
|---|---|---|---|---|---|---|
| All cases CR | CR | 10 (24.4%) | 6 (13.6%) | | | |
| | PR | 21 (51.2%) | 15 (34.1%) | | | |
| | NR | 10 (24.4%) | 23 (52.3%) | | | |
| | Yes (CR or PR) | 31 (75.6%) | 21 (47.7%) | 0.008 | 3.345 | 1.417 |
| | No (NR) | 10 (24.4%) | 23 (52.3%) | | | |
| All cases failures | CR | 4 (9.8%) | 2 (4.5%) | | | |
| | PR | 21 (51.2%) | 15 (34.1%) | | | |
| | NR | 16 (39.0%) | 27 (61.4%) | | | |
| | Yes (CR or PR) | 25 (61.0%) | 17 (38.6%) | 0.032 | 2.454 | 1.090 |
| | No (NR) | 16 (39.0%) | 27 (61.4%) | | | |
| Experimental cases failure, control arm cases CR | CR | 4 (9.8%) | 6 (13.6%) | | | |
| | PR | 21 (51.2%) | 15 (34.1%) | | | |
| | NR | 16 (39.0%) | 23 (52.3%) | | | |
| | Yes (CR or PR) | 25 (61.0%) | 21 (47.7%) | 0.157 | 1.700 | 0.760 |
| | No (NR) | 16 (39.0%) | 23 (52.3%) | | | |

Source: Table 14.2.2.1

### 11.2.2 Analysis of secondary efficacy endpoints

For secondary endpoints see Section 9.4.4.

### 11.2.3 Trilineage hematological response rate (CR and PR) at 3, 12 and 18 months

At 3 months after treatment start, according to the investigator assessment, 20/41 patients (48.8%) were reported with trilineage hematologic response in the Eltrombopag Arm and 11/44 patients (25.0%) in the Placebo Arm. The response rate was significantly higher after treatment with eltrombopag as compared to the Placebo Arm (p=0.020; OR 2.821; 95% confidence limit for OR 1.202), see Table 18.

**Table 18: Trilineage hematological response at 3 months according to investigator assessment (FAS)**

| Response assessment | Eltrombopag N=41 | | Placebo N=44 | | Comparison of treatment arms | | |
|---|---|---|---|---|---|---|---|
| **Response** | **N** | **% [95% CI]** | **N** | **% [95% CI]** | **p-value** | **OR** | **95% LL for OR** |
| CR | 2 | 4.9 [NA; NA] | 1 | 2.3 [NA; NA] | | | |
| PR | 18 | 43.9 [29.9; 59] | 10 | 22.7 [12.7; 37.2] | | | |
| NR | 21 | 51.2 [36.5; 65.7] | 33 | 75 [60.4; 85.6] | | | |
| Yes (CR or PR) | 20 | 48.8 [34.3; 63.5] | 11 | 25 [14.4; 39.6] | 0.020 | 2.821 | 1.202 |
| No (NR) | 21 | 51.2 [36.5; 65.7] | 33 | 75 [60.4; 85.6] | | | |

NA not applicable
Source: Table 14.2.3.1

For response assessments at 12 and 18 months please refer to Table 19. After 12 months, significant differences were seen between the following groups: A versus C (p=0.046, OR 0.256, 95% CI [0.042; 1.100]), A versus D (p=0.026, OR 6.448, 95% CI [1.032; 72.473]) and C versus D (p=0.001, OR 22.938, 95% CI [2.832; 329.315]). After 18 months, most significant differences were seen between the following groups: A2 versus D (p=0.019, OR 12.265, 95% CI [1.345; 610.074]) and C versus D (p=0.007, OR 13.969, 95% CI [1.492; 705.743]), see Table 14.2.3.3. For treatments in the different groups see Figure 2.

For changes in hematological response from month 6 to month 12 and 18 refer to Tables 14.2.3.4 and 14.2.3.5.

**Table 19: Trilineage hematological response at 12 and 18 months according to investigator assessment (FAS)**

| Response assessment | | NA | CR | PR | NR | CR+PR* |
|---|---|---|---|---|---|---|
| | **Arm** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** |
| After 12 months | A | 4 (10.5%) | 11 (28.9%) | 14 (36.8%) | 9 (23.7%) | 25 (65.8%) |
| | B (N=2) | 1 (50.0%) | 1 (50.0%) | -- | -- | 1 (50.0%) |
| | C (N=26) | -- | 9 (34.6%) | 14 (53.8%) | 3 (11.5%) | 23 (88.5%) |
| | D (N=9) | 7 (77.8%) | -- | 2 (22.2%) | -- | 2 (22.2%) |
| | Other | 10 (100.0%) | -- | --- | -- | -- |
| | Total (N=85) | 22 (25.9%) | 21 (24.7%) | 30 (35.3%) | 12 (14.1%) | 51 (60.0%) |
| After 18 months | A1 (N=5) | 4 (80.0%) | -- | -- | 1 (20.0%) | -- |
| | A2 (N=29) | 6 (20.7%) | 11 (37.9%) | 7 (24.1%) | 5 (17.2%) | 18 (62.1%) |
| | B (N=2) | 1 (50.0%) | 1 (50.0%) | -- | -- | 1 (50.0%) |
| | C (N=26) | 7 (26.9%) | 7 (26.9%) | 10 (38.5%) | 2 (7.7%) | 17 (65.4%) |
| | D (N=9) | 8 (88.9%) | -- | 1 (11.1%) | -- | 1 (11.1%) |
| | Other | 14 (100.0%) | --- | -- | -- | -- |
| | Total (N=85) | 40 (47.1%) | 19 (22.4%) | 18 (21.2%) | 8 (9.4%) | 37 (43.5%) |

Source: Table 14.2.3.2

### 11.2.4 Single lineage response at 3, 6, 12 and 18 months

Data for single lineage response, pairwise comparison of treatment groups and changes from month 6 to month 12 and 18 are summarized in Section 14.2.4. Comparison of eltrombopag and placebo treatment arms after 3 and 6 months is provided in Table 20.

Neutrophil response was significantly improved after 3 months of eltrombopag treatment as compared to the Placebo Arm (p=0.012; OR 2.984; 95% LL for OR 1.308). However, after 6 months, the difference between the treatment arms was no longer statistically significant different. The erythroid response showed no significant difference between the treatment arms, neither after 3 nor after 6 months. The platelet response was significantly improved after 6 months of eltrombopag treatment as compared to the Placebo Arm (p=0.034; OR 2.443; 95% LL for OR 1.081), but not yet after 3 months.

**Table 20: Single lineage response (FAS)**

| Response assessment | | No Response | | Response | | Comparison of treatment arms | | |
|---|---|---|---|---|---|---|---|---|
| Type of response | Arm | N | % [95% CI] | N | % [95% CI] | p-value | OR | 95% LL for OR |
| **Neutrophil** | | | | | | | | |
| After 3 months | Eltrombopag | 17 | 41.5 [27.7; 56.6] | 24 | 58.5 [43.4; 72.3] | 0.012 | 2.984 | 1.308 |
| | Placebo | 30 | 68.2 [53.4; 80.1] | 14 | 31.8 [19.9; 46.6] | | | |
| After 6 months | Eltrombopag | 18 | 43.9 [29.9; 59] | 23 | 56.1 [41; 70.1] | 0.118 | 1.832 | 0.821 |
| | Placebo | 26 | 59.1 [44.4; 72.3] | 18 | 40.9 [27.7; 55.6] | | | |
| **Erythroid** | | | | | | | | |
| After 3 months | Eltrombopag | 14 | 73.7 [50.9; 88.5] | 5 | 26.3 [11.5; 49.1] | 0.606 | 1.070 | 0.251 |
| | Placebo | 15 | 75.0 [52.8; 89.2] | 5 | 25.0 [10.8; 47.2] | | | |
| After 6 months | Eltrombopag | 13 | 68.4 [45.8; 84.8] | 6 | 31.6 [15.2; 54.2] | 0.714 | 0.861 | 0.227 |
| | Placebo | 13 | 65.0 [43.2; 82] | 7 | 35.0 [18.0; 56.8] | | | |
| **Platelet** | | | | | | | | |
| After 3 months | Eltrombopag | 25 | 61.0 [45.7; 74.4] | 16 | 39.0 [25.6; 54.3] | 0.179 | 1.696 | 0.719 |
| | Placebo | 32 | 72.7 [58.0; 83.8] | 12 | 27.3 [16.2; 42.0] | | | |
| After 6 months | Eltrombopag | 18 | 43.9 [29.9; 59.0] | 23 | 56.1 [41.0; 70.1] | 0.034 | 2.443 | 1.081 |
| | Placebo | 29 | 65.9 [51.1; 78.2] | 15 | 34.1 [21.8; 48.9] | | | |

Source: Table 14.2.4.1

### 11.2.5 Cumulative incidence of trilineage response

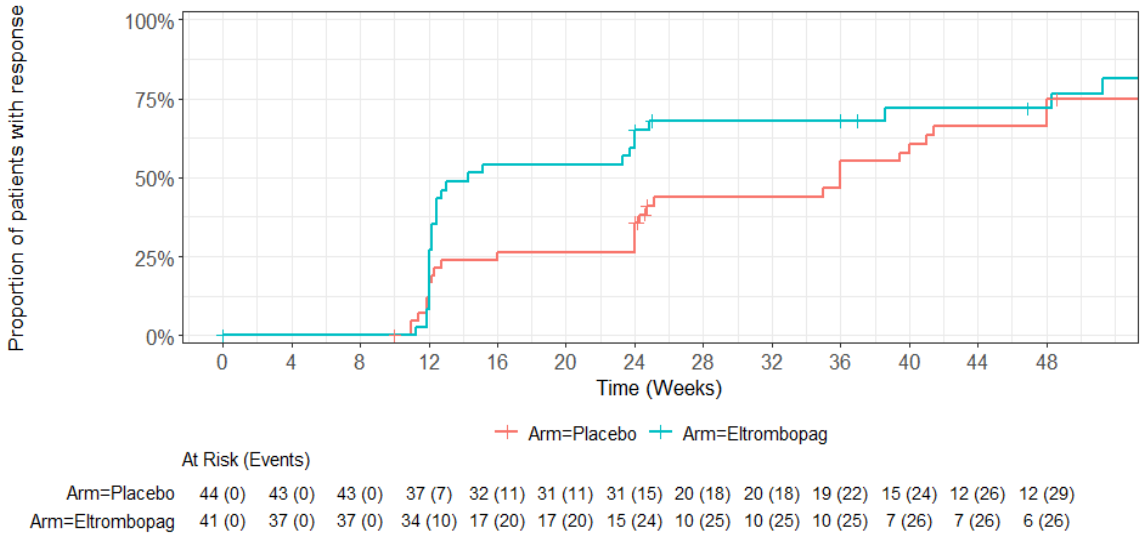
Summary results for cumulative incidence of trilineage response are provided in Section 14.2.5.

The cumulative incidence of trilineage response by treatment arm and study group is depicted in Figure 4 and Figure 5, respectively. Cumulative incidence of response at 6 months in the Eltrombopag Arm was higher than in the Placebo Arm. After response assessment and unblinding, patients in the placebo group who had not achieved CR by month 6, could have received eltrombopag in addition to ongoing CSA (Group A, n=38; see Figure 3). Four patients assigned to Group A did not receive eltrombopag. Twenty-five patients of Group A achieved

PR (n=14) or CR (n=11) by the evaluation at 12 months, i.e., 6 months of eltrombopag treatment (Figure 5). Despite this improvement by addition of eltrombopag in Group A after 6 months, the cumulative incidence of trilineage response was superior in patients who had been initially randomized to eltrombopag (HR 1.71; p=0.039) see Table 14.2.5.1.

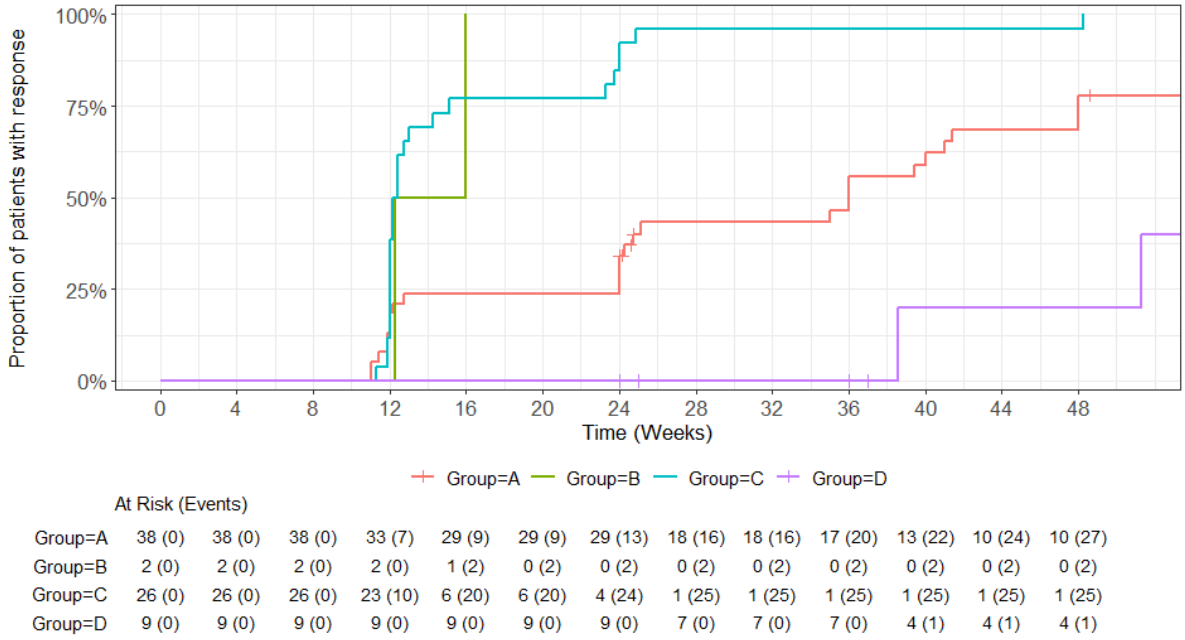
The subgroup analysis showed evidence for a lower incidence of trilineage response in patients older than 60 years with transfusion-dependent MAA (HR 0.41; p=0.016), see Table 14.2.5.1.

**Figure 4: Cumulative incidence of trilineage response by study arm (FAS)**




Source: Figure 14.2.5.1

**Figure 5: Cumulative incidence of trilineage response by study group (FAS)**




Source: Figure 14.2.5.2

### 11.2.6 Time to best hematological and single lineage response

The median time to best trilineage response for patients with response in the FAS population was 8.31 months. The median time to reach single lineage response was 7.08 months (erythroid), 5.52 months (platelet) and 2.91 months (neutrophil). A significant difference between the Placebo and Eltrombopag Arm was observed only for neutrophil response (p=0.025), see Table 21 and Table 14.2.5.3.

**Table 21: Time to response (FAS)**

| Time to… (months) | | Eltrombopag | Placebo | Total |
|---|---|---|---|---|
| Best trilineage response | N | 30 | 31 | 61 |
| | Arithmetic mean / STD | 9.35 / 8.21 | 10.62 / 6.88 | 10.00 / 7.53 |
| | Median (IQR) | 6.95 (2.89-11.20) | 9.20 (8.28-11.15) | 8.31 (5.49-11.24) |
| | Range | 2.6 – 36.8 | 2.7 – 38.6 | 2.6 – 38.6 |
| Erythroid response | N | 26 | 32 | 58 |
| | Arithmetic mean / STD | 8.47 / 7.99 | 8.58 / 7.39 | 8.53 / 7.59 |
| | Median (IQR) | 5.59 (2.81-8.53) | 8.28 (2.82-9.43) | 7.08 (2.80-9.37) |
| | Range | 2.8 – 35.6 | 2.6 – 38.6 | 2.6 – 38.6 |
| Platelet response | N | 28 | 33 | 61 |
| | Arithmetic mean / STD | 5.32 / 4.29 | 6.89 / 4.17 | 6.17 / 4.26 |
| | Median (IQR) | 2.92 (2.76-5.72) | 5.68 (2.79-9.43) | 5.52 (2.76-8.97) |
| | Range | 2.7 – 22.1 | 2.5 – 21.8 | 2.5 – 22.1 |

| Time to… (months) | | Eltrombopag | Placebo | Total |
|---|---|---|---|---|
| Neutrophil response | N | 32 | 34 | 66 |
| | Arithmetic mean / STD | 4.13 / 3.62 | 6.51 / 4.74 | 5.36 / 4.37 |
| | Median (IQR) | 2.79 (2.76-3.99) | 5.52 (2.77-8.33) | 2.91 (2.76-5.69) |
| | Range | 2.6 – 22.4 | 2.5 – 21.8 | 2.5 – 22.4 |

Source: Table 14.2.5.3

### 11.2.7 Proportion of patients with need for transfusions and number of units transfused

There was no significant difference between the treatment arms in the proportion of patients requiring transfusions (Table 14.2.6.1) and in the number of transfused units (Table 14.2.6.2). In the FAS population, a median number of 6 units of PC and 7 units of pRBC were transfused within the first 6 months, see Table 22.

**Table 22: Number of units transfused within the first 6 months (FAS)**

| Parameter | | Eltrombopag | Placebo | Total |
|---|---|---|---|---|
| Any | N | 29 | 31 | 60 |
| | Arithmetic mean / STD | 15.5 / 17.4 | 17.9 / 16.9 | 16.7 / 17.1 |
| | Median (IQR) | 8.0 (5.0-17.0) | 11.0 (4.5-32.0) | 9.5 (5.0-25.0) |
| | Range | 1 - 77 | 1 - 62 | 1 - 77 |
| PC | N | 25 | 20 | 45 |
| | Arithmetic mean / STD | 9.2 / 11.0 | 14.0 / 12.6 | 11.3 / 11.9 |
| | Median (IQR) | 4.0 (3.0-12.0) | 12.0 (3.2-20.2) | 6.0 (3.0-17.0) |
| | Range | 1 - 43 | 1 - 43 | 1 – 43 |
| pRBC | N | 26 | 27 | 53 |
| | Arithmetic mean / STD | 8.5 / 8.6 | 10.2 / 6.9 | 9.3 / 7.7 |
| | Median (IQR) | 6.0 (2.0-10.8) | 9.0 (5.5-15.0) | 7.0 (2.0-14.0) |
| | Range | 1 - 39 | 1 - 28 | 1 - 39 |

Source: Table 14.2.6.2

### 11.2.8 Cumulative incidence of progression to SAA/VSAA or intensive immunosuppressive treatment with ATG

Data for cumulative incidence of progress to SAA/VSAA or intensive immunosuppressive treatment with ATG are summarized in Section 14.2.7. Two cases of progression were reported in the Eltrombopag Arm after evaluation of the primary endpoint whereas no such case was observed in the Placebo Arm.

### 11.2.9 Toxicity profile as measured using the CTCAE criteria

No TEAEs of Grade 4 or 5 were observed within the first 6 months after therapy start.

The number of patients experiencing TEAEs of Grade 3 by SOC and PT are listed in Table 23 (first 10 weeks) and Table 24 (between 10 weeks and 6 months). For number of events refer to Tables 14.3.2.5, 14.3.2.6, 14.3.4.5 and 14.3.4.6.

The following TEAEs of Grade 3 occurring during the first 10 weeks of treatment were assessed as related to the study medication: hypertension (1 patient each in the Eltrombopag and Placebo Arm), decreased platelet count (1 patient in the Placebo Arm) and paresthesia (1 patient in the Placebo Arm), see Table 14.3.1.6.

TEAEs of Grade 3 reported between 10 weeks and 6 months and assessed as related to the study medication were hypertension (1 patient in the Placebo Arm) and decreased platelet count (1 patient in the Eltrombopag Arm), see Table 14.3.3.6.

No TEAEs of Grade 5 were reported beyond 6 months after treatment initiation. A total of 15 patients (19.5%) experienced Grade 3 and 4 TEAEs of which stomatitis (1 patient), maculo-papular rash (1 patient) and thrombosis (1 patient) were assessed as related to study treatment (Tables 14.3.5.5 and 14.3.5.6). For number of events please refer to Tables 14.3.6.5 and 14.3.6.6.

**Table 23: Number of patients with TEAEs of CTCAE Grade 3 within the first 10 weeks by SOC and PT (SAF)**

| Number of subjects with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| **SOC** | **N** | **%** | **N** | **%** | **N** | **%** |
| Total | 4 | 11.1 | 7 | 17.1 | 11 | 14.3 |
| Nervous system disorders | 2 | 5.6 | 1 | 2.4 | 3 | 3.9 |
| Headache | 2 | 5.6 | 0 | 0.0 | 2 | 2.6 |
| Paresthesia | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Gastrointestinal disorders | 1 | 2.8 | 1 | 2.4 | 2 | 2.6 |
| Gingival bleeding | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Abdominal pain | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Vascular disorders | 1 | 2.8 | 1 | 2.4 | 2 | 2.6 |
| Hypertension | 1 | 2.8 | 1 | 2.4 | 2 | 2.6 |
| Infections and infestations | 0 | 0.0 | 2 | 4.9 | 2 | 2.6 |
| Meningitis | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Appendicitis | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Investigations | 0 | 0.0 | 2 | 4.9 | 2 | 2.6 |
| Platelet count decreased | 0 | 0.0 | 2 | 4.9 | 2 | 2.6 |
| Blood and lymphatic system disorders | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Anemia | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| General disorders and administration site conditions | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Fatigue | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Metabolism and nutrition disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Hyperkalemia | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Surgical and medical procedures | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Tooth extraction | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |

Source: Table 14.3.1.5

**Table 24: Number of patients with TEAEs of CTCAE Grade 3 between 10 weeks and 6 months by SOC and PT (SAF)**

| Number of subjects with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| **SOC** | **N** | **%** | **N** | **%** | **N** | **%** |
| Total | 4 | 11.1 | 3 | 7.3 | 7 | 9.1 |
| Nervous system disorders | 0 | 0.0 | 2 | 4.9 | 2 | 2.6 |
| Cerebral venous thrombosis | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Headache | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Cardiac disorders | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Myocardial infarction | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| General disorders and administration site conditions | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Condition aggravated | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Infections and infestations | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| COVID-19 pneumonia | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Investigations | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Platelet count decreased | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Vascular disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Hypertension | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |

Source: Table 14.3.3.5

### 11.2.10 Relapse rate at 6, 12 and 18 months

Data on relapse rates at 6, 12 and 18 months are summarized in Section 14.2.8. and Table 25. Comparison of treatment arms revealed a significant difference with respect to the relapse rate at 6 months (p=0.024).

**Table 25: Relapse rates from best trilineage response (FAS)**

| Response assessment | | Relapse | | No Relapse | | Comparison of treatment arms |
|---|---|---|---|---|---|---|
| **Time** | **Arm** | **N** | **% [95% CI]** | **N** | **% [95% CI]** | **p-Value** |
| ≤ 24 weeks | Eltrombopag | 5 | 16.7 [6.9; 34] | 25 | 83.3 [66; 93.1] | 0.024 |
| | Placebo | 0 | NA | 31 | 100 [86.9; 100] | |
| ≤ 48 weeks | A | 3 | 10.7 [2.9; 28] | 25 | 89.3 [72; 97.1] | |
| | B | 1 | 50 [9.5; 90.5] | 1 | 50 [9.5; 90.5] | |
| | C | 10 | 38.5 [22.4; 57.5] | 16 | 61.5 [42.5; 77.6] | |
| | D | 0 | NA | 4 | 100 [45.4; 100] | |
| | Other | 0 | NA | 1 | 100 [16.7; 100] | |
| ≤ 72 weeks | A1 | 1 | 50 [9.5; 90.5] | 1 | 50 [9.5; 90.5] | |
| | A2 | 9 | 34.6 [19.3; 53.9] | 17 | 65.4 [46.1; 80.7] | |
| | B | 1 | 50 [9.5; 90.5] | 1 | 50 [9.5; 90.5] | |
| | C | 10 | 38.5 [22.4; 57.5] | 16 | 61.5 [42.5; 77.6] | |

| Response assessment | | Relapse | | No Relapse | | Comparison of treatment arms |
|---|---|---|---|---|---|---|
| **Time** | **Arm** | **N** | **% [95% CI]** | **N** | **% [95% CI]** | **p-Value** |
| | D | 0 | NA | 4 | 100 [45.4; 100] | |
| | Other | 0 | NA | 1 | 100 [16.7; 100] | |

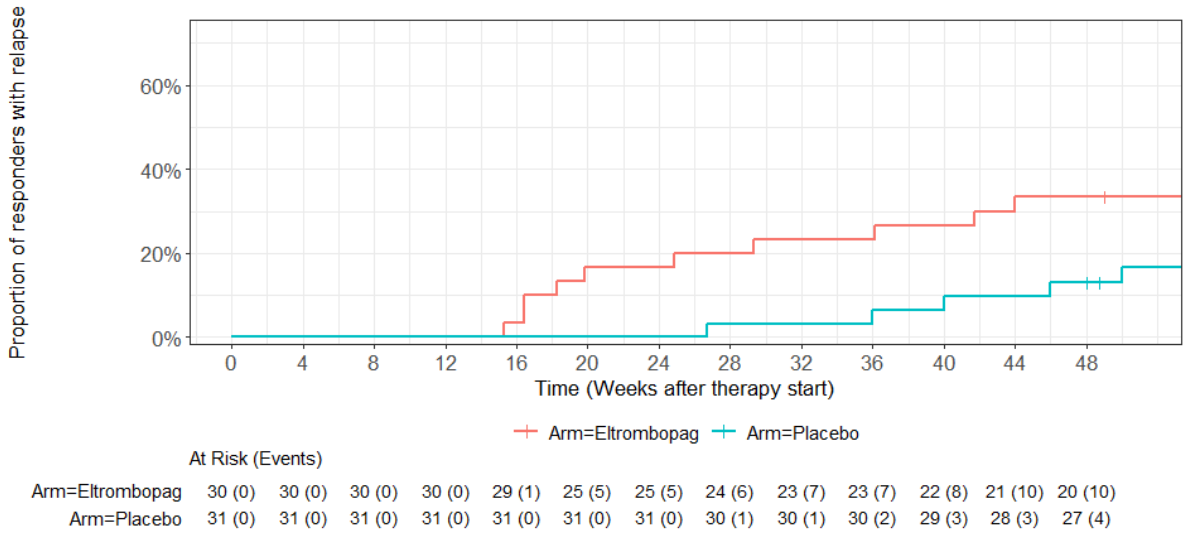
NA not applicable
Source: Table 14.2.8.1

### 11.2.11 Cumulative incidence of relapse (from best hematological response)

The proportion of responders with relapse tended to be higher in the Eltrombopag Arm (see Figure 6). However, comparison of treatment arms and subgroup analysis did not show a statistically significant difference. In relation to the duration of eltrombopag therapy, the number of recurrences after 6 months of eltrombopag therapy was approximately the same (5 versus 4 patients).

Cumulative incidence of relapse by study group is illustrated in Figure 14.2.9.3. Results of the subgroup analysis and pairwise comparison between treatment groups are provided in Tables 14.2.9.1 to 14.2.9.4.

**Figure 6: Cumulative incidence of relapse by study arm (FAS)**



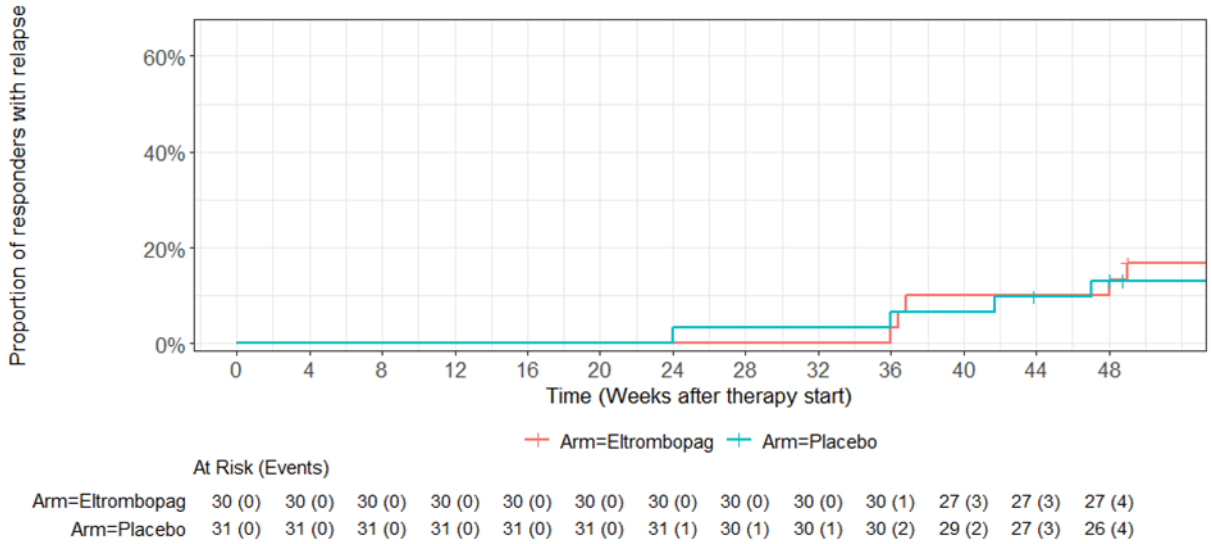

Source: Figure 14.2.9.1

### 11.2.12 Cumulative incidence of relapse (from best hematological response, modified criteria)

The relapse definition was very broad and included also minor, clinically not significant declines of blood counts when still response criteria were fulfilled. Therefore, additionally a post-hoc analysis with modified relapse criteria was performed. Relapse from first trilineage response was defined as no longer meeting criteria for at least PR (i.e., patients must have received at least PR – and the next assessment which did no longer fulfill criteria for at least PR was considered as relapse (modified criteria). This is a common relapse definition in AA trials and

allows better comparison to results of other trials. This analysis did not show a significant difference in relapse rate by treatment arm.

**Figure 7: Cumulative incidence of relapse by study arm – modified criteria (FAS)**




Source: Figure 14.2.9.2

### 11.2.13 Overall survival (OS)

Three cases of death were reported, all occurred in the Eltrombopag Arm. Median OS could not be calculated. Further details are given in Section 14.2.11. Please also refer to Section 12.4 for further description of cases of death.

### 11.2.14 Failure free survival (FFS)

FFS by study arm and study group is illustrated in Figure 8 and Figure 14.2.10.3, respectively. No significant difference was found between treatment arms (p=0.872). The median FFS was 24.86 weeks (95% CI 24.00; 87.29) in the Eltrombopag Arm and 24.29 weeks (95% CI 24.00; 36.00) in the Placebo Arm (Table 14.2.10.1).

Applying modified relapse criteria, the median FFS was 49.00 weeks (95% CI 24.43; NA) in the Eltrombopag Arm and 24.29 weeks (95% CI 24.00; 41.71) in the Placebo Arm (Table 14.2.10.2), see Figure 9. However, the difference did also not reach statistical significance (p=0.187).

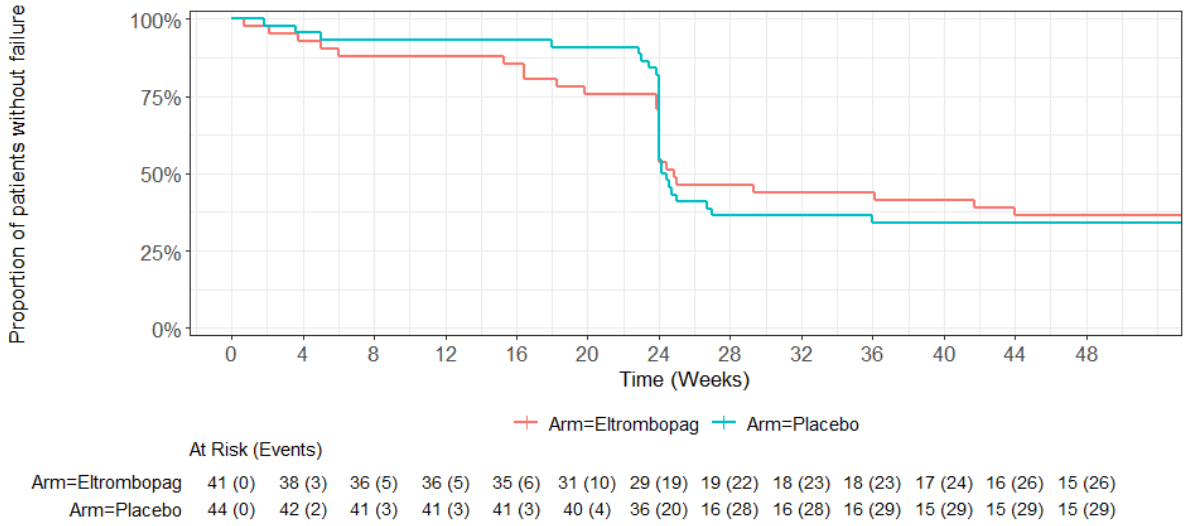
Pairwise comparison revealed a significant difference in groups A versus D (p=0.015), B versus D (p=0.009) and C versus D (p=0.001) (Table 14.2.10.4). The median FFS was longest in Group C with 99.00 weeks (Table 26).

**Table 26: Median FFS per group**

| Group | Median (weeks) | 95% CI |
|---|---|---|
| A | 24.50 | [24.00; 56.14] |
| B | 36.00 | [36.00; NA] |
| C | 99.00 | [36.14; NA] |
| D | 24.00 | [24.00; 24.00] |

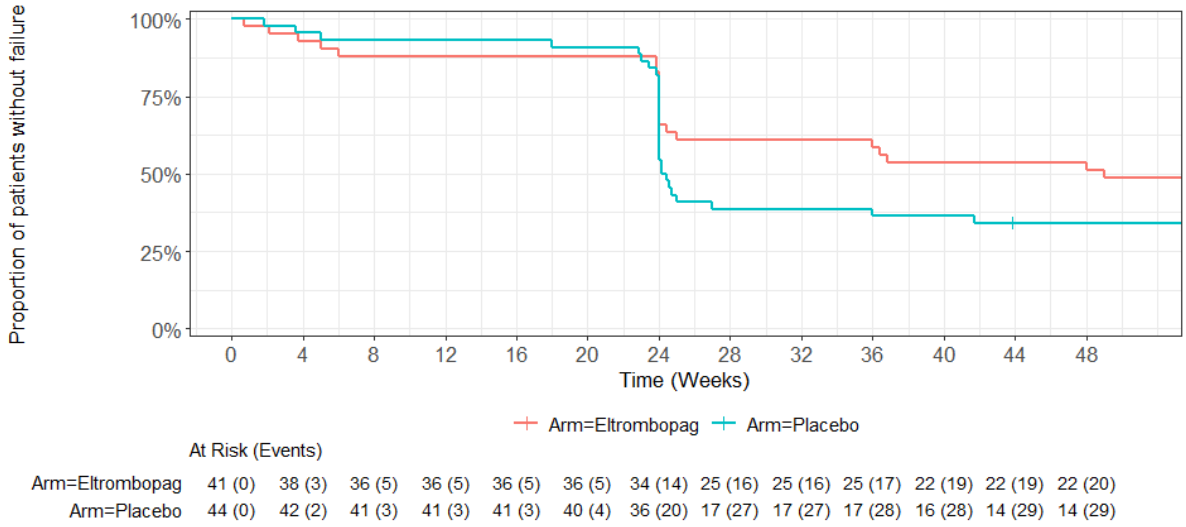
Source: Table 14.2.10.3

**Figure 8: FFS by study arm (FAS)**




Source: Figure 14.2.10.1

**Figure 9: FFS by study arm – modified relapse criteria (FAS)**




Source: Figure 14.2.10.2

### 11.2.15 Telomere lengths and presence of telomerase mutations as biomarkers for response

Summary results for evaluation of telomere lengths are given in Table 14.2.12.1. Telomere length was not associated with probability of trilineage hematologic response.

### 11.2.16 Quality of life (QoL).

QoL data are summarized in Section 14.4.

#### 11.2.16.1 EORTC QLQ-C30

Overall, 75/85 patients in the FAS population (88.2%) completed the QLQ-C30 questionnaire at therapy start and 73/85 patients (85.9%) after 6 months of treatment. Further details on compliance at later timepoints and distribution between study arms and study groups can be found in Tables 14.4.1.1 and 14.4.1.2. Profiles of mean scores over time are depicted in Figure 14.4.1.1 and Figure 14.4.1.2. Changes in scores over time are shown in Figures 14.4.1.3 to 14.4.1.18. Summary statistics of original scores and changes from baseline are provided in Tables 14.4.1.3 to 14.4.1.6.

Data for QLQ scores at therapy start and after 24 weeks of treatment with eltrombopag or placebo are summarized in Table 27. The global health status had improved in 23.5% of patients and the QoL summary score in 15.3% of patients. Among the different scales, cognitive functioning had improved in 32.9% of patients with a significant higher rate of improvement in the Eltrombopag Arm (48.8% versus 18.2%). Role functioning, social functioning and fatigue had improved in the majority of patients independent of the treatment. In the other scales, the majority of patients reported no change. A total of 18.8% of patients reported improvement of financial difficulties with a significant higher rate in the eltrombopag group (31.7% versus 6.8%). For further details see Table 28.

**Table 27: QLQ-C30 scales by treatment arm (FAS)**

| | | Eltrombopag | Placebo | Total |
|---|---|---|---|---|
| Global health status / QoL | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 74.2 / 19.0 | 67.6 / 17.5 | 70.8 / 18.4 |
| | Range | 25.6 – 100.0 | 28.5 – 96.8 | 25.6 – 100.0 |
| 24 weeks | N | 33 | 37 | 70 |
| | Arithmetic mean / STD | 73.4 / 19.0 | 67.8 / 18.4 | 70.4 / 18.8 |
| | Range | 37.1 – 100.0 | 36.5 – 100.0 | 36.5 – 100.0 |
| QoL summary score | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 53.9 / 22.5 | 47.3 / 23.1 | 50.5 / 22.9 |
| | Range | 8.3 – 91.7 | 0.0 – 83.3 | 0.0 – 91.7 |
| 24 weeks | N | 34 | 38 | 72 |
| | Arithmetic mean / STD | 58.3 / 21.4 | 57.0 / 18.8 | 57.6 / 20.0 |
| | Range | 16.7 – 100.0 | 8.3 – 83.3 | 8.3 – 100.0 |

| | | Eltrombopag | Placebo | Total |
|---|---|---|---|---|
| Cognitive functioning | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 73.5 / 26.6 | 73.0 / 25.9 | 73.2 / 26.0 |
| | Range | 16.7 – 100.0 | 16.7 – 100.0 | 16.7 – 100.0 |
| 24 weeks | N | 34 | 38 | 72 |
| | Arithmetic mean / STD | 75.5 / 24.4 | 63.6 / 27.6 | 69.2 / 26.6 |
| | Range | 16.7 – 100.0 | 16.7 – 100.0 | 16.7 -100.0 |
| Emotional functioning | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 61.2 / 31.2 | 57.1 / 29.5 | 59.0 / 30.2 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| 24 weeks | N | 34 | 38 | 72 |
| | Arithmetic mean / STD | 59.8 / 26.5 | 56.1 / 25.7 | 57.9 / 26.0 |
| | Range | 0.0 – 100.0 | 8.3 – 100.0 | 0.0 – 100.0 |
| Physical functioning | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 70.7 / 23.2 | 63.2 / 21.3 | 66.8 / 22.4 |
| | Range | 0.0 – 100.0 | 20.0 – 100.0 | 0.0 – 100.0 |
| 24 weeks | N | 34 | 38 | 72 |
| | Arithmetic mean / STD | 71.8 / 22.2 | 64.8 / 20.3 | 68.1 / 21.4 |
| | Range | 13.3 – 100.0 | 26.7 – 100.0 | 13.3 – 100.0 |
| Role functioning | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 56.9 / 30.7 | 50.0 / 28.6 | 53.3 / 29.6 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| 24 weeks | N | 34 | 38 | 72 |
| | Arithmetic mean / STD | 57.4 / 31.3 | 47.8 / 30.3 | 52.3 / 30.9 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| Social functioning | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 64.7 / 30.6 | 59.0 / 32.2 | 61.7 / 31.4 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| 24 weeks | N | 34 | 38 | 72 |
| | Arithmetic mean / STD | 56.4 / 32.0 | 57.0 / 29.9 | 56.7 / 30.7 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 -100.0 |
| Fatigue | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 44.8 / 33.4 | 55.3 / 29.0 | 50.2 / 31.4 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| 24 weeks | N | 34 | 38 | 72 |
| | Arithmetic mean / STD | 40.5 / 29.7 | 49.9 / 25.3 | 45.4 / 27.7 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| Nausea and vomiting | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 2.5 / 7.3 | 11.3 / 17.6 | 7.0 / 14.3 |
| | Range | 0.0 – 33.3 | 0.0 – 83.3 | 0.0 – 83.3 |
| 24 weeks | N | 34 | 38 | 72 |
| | Arithmetic mean / STD | 12.3 / 20.2 | 11.4 / 15.1 | 11.8 / 17.6 |

| | | Eltrombopag | Placebo | Total |
|---|---|---|---|---|
| | Range | 0.0 – 83.3 | 0.0 – 50.0 | 0.0 – 83.3 |
| Pain | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 18.6 / 29.5 | 29.7 / 30.2 | 24.4 / 30.2 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| 24 weeks | N | 34 | 38 | 72 |
| | Arithmetic mean / STD | 27.9 / 30.1 | 32.0 / 32.7 | 30.1 / 31.4 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| Dyspnea | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 43.1 / 37.2 | 59.5 / 26.2 | 51.6 / 32.8 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| 24 weeks | N | 34 | 38 | 72 |
| | Arithmetic mean / STD | 32.4 / 31.2 | 53.5 / 33.4 | 43.5 / 33.9 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| Insomnia | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 28.4 / 33.0 | 38.7 / 38.1 | 33.8 / 35.9 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| 24 weeks | N | 34 | 38 | 72 |
| | Arithmetic mean / STD | 22.5 / 30.4 | 36.8 / 37.0 | 30.1 / 34.6 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| Appetite loss | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 12.7 / 21.7 | 13.5 / 22.9 | 13.1 / 22.2 |
| | Range | 0.0 – 66.7 | 0.0 – 66.7 | 0.0 – 66.7 |
| 24 weeks | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 10.8 / 19.6 | 17.1 / 25.6 | 14.1 / 23.0 |
| | Range | 0.0 – 66.7 | 0.0 – 66.7 | 0.0 – 66.7 |
| Constipation | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 3.9 / 17.9 | 9.9 / 24.7 | 7.0 / 21.8 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 - 100.0 |
| 24 weeks | N | 34 | 38 | 72 |
| | Arithmetic mean / STD | 3.9 / 13.6 | 6.1 / 17.1 | 5.1 / 15.5 |
| | Range | 0.0 – 66.7 | 0.0 – 66.7 | 0.0 – 66.7 |
| Diarrhea | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 8.8 / 20.6 | 5.4 / 16.7 | 7.0 / 18.6 |
| | Range | 0.0 – 66.7 | 0.0 – 66.7 | 0.0 – 66.7 |
| 24 weeks | N | 33 | 38 | 71 |
| | Arithmetic mean / STD | 17.2 / 29.0 | 11.4 / 24.8 | 14.1 / 26.8 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| Financial difficulties | | | | |
| Therapy start | N | 34 | 35 | 69 |
| | Arithmetic mean / STD | 22.5 / 29.3 | 17.1 / 24.7 | 19.8 / 27.0 |
| | Range | 0.0 -100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| 24 weeks | N | 33 | 38 | 71 |

| | | Eltrombopag | Placebo | Total |
|---|---|---|---|---|
| | Arithmetic mean / STD | 20.2 / 30.0 | 31.6 / 37.1 | 26.3 / 34.2 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |

Source: Table 14.4.1.3

**Table 28: QLQ-C30 scales by treatment arm at 24 weeks after start of treatment, changes from baseline (FAS)**

| Number of patients N (%) | | Eltrombopag | Placebo | Total |
|---|---|---|---|---|
| Global health status / QoL | Improvement | 11 (26.8%) | 9 (20.5%) | 20 (23.5%) |
| | No change | 22 (53.7%) | 16 (36.4%) | 38 (44.7%) |
| | Deterioration | 7 (17.1%) | 9 (20.5%) | 16 (18.8%) |
| | Comparison between treatment arms | p=0.561 | | |
| QoL summary score | Improvement | 6 (14.6%) | 7 (15.9%) | 13 (15.3%) |
| | No change | 22 (53.7%) | 17 (38.6%) | 39 (45.9%) |
| | Deterioration | 6 (14.6%) | 8 (18.2%) | 14 (16.5%) |
| | Comparison between treatment arms | p=0.951 | | |
| Cognitive functioning | Improvement | 20 (48.8%) | 8 (18.2%) | 28 (32.9%) |
| | No change | 9 (22.0%) | 17 (38.6%) | 26 (30.6%) |
| | Deterioration | 6 (14.6%) | 8 (18.2%) | 14 (16.5%) |
| | Comparison between treatment arms | p=0.021 | | |
| Emotional functioning | Improvement | 12 (29.3%) | 11 (25.0%) | 23 (27.1%) |
| | No change | 17 (41.5%) | 13 (29.5%) | 30 (35.3%) |
| | Deterioration | 6 (14.6%) | 8 (18.2%) | 14 (16.5%) |
| | Comparison between treatment arms | p=1.000 | | |
| Physical functioning | Improvement | 12 (29.3%) | 10 (22.7%) | 22 (25.9%) |
| | No change | 17 (41.5%) | 13 (29.5%) | 30 (35.3%) |
| | Deterioration | 6 (14.6%) | 8 (18.2%) | 14 (16.5%) |
| | Comparison between treatment arms | p=0.919 | | |
| Role functioning | Improvement | 15 (36.6%) | 12 (27.3%) | 27 (31.8%) |
| | No change | 11 (26.8%) | 8 (18.2%) | 19 (22.4%) |
| | Deterioration | 6 (14.6%) | 8 (18.2%) | 14 (16.5%) |
| | Comparison between treatment arms | p=0.893 | | |
| Social functioning | Improvement | 13 (31.7%) | 17 (38.6%) | 30 (35.3%) |
| | No change | 15 (36.6%) | 11 (25.0%) | 26 (30.6%) |
| | Deterioration | 6 (14.6%) | 8 (18.2%) | 14 (16.5%) |
| | Comparison between treatment arms | p=0.356 | | |
| Fatigue | Improvement | 15 (36.6%) | 15 (34.1%) | 30 (35.3%) |
| | No change | 9 (22.0%) | 7 (15.9%) | 16 (18.8%) |
| | Deterioration | 6 (14.6%) | 8 (18.2%) | 14 (16.5%) |
| | Comparison between treatment arms | p=0.891 | | |

| Number of patients N (%) | | Eltrombopag | Placebo | Total |
|---|---|---|---|---|
| Nausea and vomiting | Improvement | 9 (22.0%) | 10 (22.7%) | 19 (22.4%) |
| | No change | 24 (58.5%) | 21 (47.7%) | 45 (52.9%) |
| | Deterioration | 6 (14.6%) | 8 (18.2%) | 14 (16.5%) |
| | Comparison between treatment arms | p=0.638 | | |
| Pain | Improvement | 15 (36.6%) | 17 (38.6%) | 32 (37.6%) |
| | No change | 19 (46.3%) | 15 (34.1%) | 34 (40.0%) |
| | Deterioration | 6 (14.6%) | 8 (18.2%) | 14 (16.5%) |
| | Comparison between treatment arms | p=0.466 | | |
| Dyspnea | Improvement | 10 (24.4%) | 6 (13.6%) | 16 (18.8%) |
| | No change | 16 (39.0%) | 14 (31.8%) | 30 (35.3%) |
| | Deterioration | 6 (14.6%) | 8 (18.2%) | 14 (16.5%) |
| | Comparison between treatment arms | p=0.679 | | |
| Insomnia | Improvement | 11 (26.8%) | 6 (13.6%) | 17 (20.0%) |
| | No change | 17 (41.5%) | 16 (36.4%) | 33 (38.8%) |
| | Deterioration | 6 (14.6%) | 8 (18.2%) | 14 (16.5%) |
| | Comparison between treatment arms | p=0.515 | | |
| Appetite loss | Improvement | 11 (26.8%) | 5 (11.4%) | 16 (18.8%) |
| | No change | 22 (53.7%) | 24 (54.5%) | 46 (54.1%) |
| | Deterioration | 7 (17.1%) | 8 (18.2%) | 15 (17.6%) |
| | Comparison between treatment arms | p=0.335 | | |
| Constipation | Improvement | 3 (7.3%) | 1 (2.3%) | 4 (4.7%) |
| | No change | 32 (78.0%) | 30 (68.2%) | 62 (72.9%) |
| | Deterioration | 6 (14.6%) | 8 (18.2%) | 14 (16.5%) |
| | Comparison between treatment arms | p=0.755 | | |
| Diarrhea | Improvement | 7 (17.1%) | 6 (13.6%) | 13 (15.3%) |
| | No change | 29 (70.7%) | 24 (54.5%) | 53 (62.4%) |
| | Deterioration | 6 (14.6%) | 9 (20.5%) | 15 (17.6%) |
| | Comparison between treatment arms | p=1.000 | | |
| Financial difficulties | Improvement | 13 (31.7%) | 3 (6.8%) | 16 (18.8%) |
| | No change | 23 (56.1%) | 25 (56.8%) | 48 (56.5%) |
| | Deterioration | 6 (14.6%) | 9 (20.5%) | 15 (17.6%) |
| | Comparison between treatment arms | p=0.024 | | |

Source: Table 14.4.1.5

### 11.2.16.2 FACIT-F

Profiles of FACIT-F mean scores and changes over time are shown in Figure 14.4.2.1 and Figure 14.4.2.2. Summary statistics of original scores and changes from baseline are provided in Tables 14.4.2.1 and 14.4.2.2, respectively.

The mean FACIT-F score for all patients of the FAS population was 19.6 at therapy start and

decreased during treatment with eltrombopag or placebo by 1.3 as compared to the baseline with no obvious difference between the treatment arms (Table 29).

**Table 29: FACIT-F scores by treatment arm (FAS)**

| | | Eltrombopag | Placebo | Total |
|---|---|---|---|---|
| Original data | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 17.5 / 12.4 | 21.5 / 12.2 | 19.6 / 12.4 |
| | Range | 0.0 – 41.0 | 1.0 – 48.0 | 0.0 – 48.0 |
| 24 weeks | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 16.5 / 12.6 | 19.2 / 10.9 | 17.9 / 11.7 |
| | Range | 1.0 – 43.0 | 1.0 – 44.0 | 1.0 – 44.0 |
| Changes from baseline | | | | |
| 24 weeks | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | -1.5 / 11.3 | -1.2 / 10.8 | -1.3 / 11.0 |
| | Range | -27.0 – 15.0 | -25.0 – 26.0 | -27.0 – 26.0 |

Source: Table 14.4.2.1 and Table 14.4.2.2

### 11.2.16.3 QLQ-AA/PNH

Profiles of QLQ-AA/PNH mean scores over time are given in Figure 14.4.3.1 and Figure 14.4.3.2. Changes in scores over time are shown in Figures 14.4.3.3 to 14.4.3.14. Summary statistics of original scores are provided in Tables 14.4.3.1 (first 6 months) and 14.4.3.2 (beyond 6 months). Changes from baseline are given in Tables 14.4.3.3 (first 6 months) and 14.4.3.4 (beyond 6 months).

Data for QLQ-AA/PNH scales at therapy start and after 24 weeks of treatment with eltrombopag or placebo are summarized in Table 30. Among the different scales, infections had improved in 27.1% of patients with a significant higher rate of improvement in the Eltrombopag Arm (41.5% versus 13.6%). However, for all scales, the majority of patients reported no change from baseline to 24 weeks after treatment start. Further details are given in Table 31.

**Table 30: QLQ-AA/PNH scales by treatment arm (FAS)**

| | | Eltrombopag | Placebo | Total |
|---|---|---|---|---|
| Body image | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 43.6 / 24.3 | 44.6 / 27.5 | 44.1 / 25.8 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| 24 weeks | N | 34 | 38 | 72 |
| | Arithmetic mean / STD | 40.7 / 26.3 | 43.0 / 21.8 | 41.9 / 23.9 |
| | Range | 0.0 – 100.0 | 0.0 – 83.3 | 0.0 – 100.0 |

| | | Eltrombopag | Placebo | Total |
|---|---|---|---|---|
| Cognitive functioning | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 31.4 / 34.8 | 33.3 / 30.4 | 32.4 / 32.4 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| 24 weeks | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 31.4 / 29.5 | 38.7 / 28.9 | 35.2 / 29.2 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| Emotional functioning | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 43.7 / 25.5 | 48.6 / 28.1 | 46.3 / 26.8 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| 24 weeks | N | 34 | 38 | 72 |
| | Arithmetic mean / STD | 41.4 / 28.8 | 44.7 / 26.8 | 43.1 / 27.6 |
| | Range | 0.0 – 93.3 | 0.0 – 100.0 | 0.0 – 100.0 |
| Fatigue | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 36.2 / 28.2 | 47.9 / 26.1 | 42.3 / 27.5 |
| | Range | 0.0 – 100.0 | 6.7 – 100.0 | 0.0 – 100.0 |
| 24 weeks | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 33.7 / 25.8 | 42.8 / 24.4 | 38.5 / 25.3 |
| | Range | 0.0 – 93.3 | 0.0 – 91.7 | 0.0 – 93.3 |
| Illness intrusiveness | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 42.1 / 21.9 | 48.1 / 27.1 | 45.3 / 24.8 |
| | Range | 3.7 – 92.6 | 0.0 – 92.6 | 0.0 – 92.6 |
| 24 weeks | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 42.9 / 26.8 | 45.1 / 24.1 | 44.0 / 25.3 |
| | Range | 0.0 – 100.0 | 0.0 – 92.6 | 0.0 – 100.0 |
| Infections | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 27.9 / 23.5 | 28.8 / 30.8 | 28.4 / 27.4 |
| | Range | 0.0 – 83.3 | 0.0 – 100.0 | 0.0 – 100.0 |
| 24 weeks | N | 34 | 38 | 72 |
| | Arithmetic mean / STD | 26.5 / 23.6 | 30.7 / 25.9 | 28.7 / 24.7 |
| | Range | 0.0 – 83.3 | 0.0 – 100.0 | 0.0 – 100.0 |
| Other symptoms | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 25.6 / 20.2 | 38.2 / 21.8 | 32.2 / 21.9 |
| | Range | 0.0 – 71.4 | 0.0 – 90.5 | 0.0 – 90.5 |
| 24 weeks | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 25.0 / 18.3 | 33.0 / 19.6 | 29.2 / 19.3 |
| | Range | 0.0 – 66.7 | 0.0 – 76.2 | 0.0 – 76.2 |
| Fear of progression | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 55.5 / 30.5 | 55.3 / 28.9 | 55.4 / 29.5 |
| | Range | 4.8 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| 24 weeks | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 49.3 / 36.3 | 49.8 / 26.6 | 49.6 / 31.4 |

| | | Eltrombopag | Placebo | Total |
|---|---|---|---|---|
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| Physical functioning | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 35.6 / 28.9 | 49.5 / 30.6 | 42.9 / 30.4 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| 24 weeks | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 35.6 / 30.4 | 50.2 / 29.6 | 43.2 / 30.7 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| Role functioning | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 39.3 / 20.4 | 47.4 / 23.6 | 43.5 / 22.4 |
| | Range | 0.0 – 90.5 | 0.0 – 85.7 | 0.0 – 90.5 |
| 24 weeks | N | 34 | 38 | 72 |
| | Arithmetic mean / STD | 41.2 / 23.8 | 48.4 / 23.2 | 45.0 / 23.6 |
| | Range | 0.0 – 85.7 | 0.0 – 90.5 | 0.0 – 90.5 |
| Social support | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 44.1 / 20.1 | 37.4 / 21.7 | 40.6 / 21.0 |
| | Range | 0.0 – 100.0 | 0.0 – 83.3 | 0.0 – 100.0 |
| 24 weeks | N | 34 | 38 | 72 |
| | Arithmetic mean / STD | 39.7 / 25.0 | 45.6 / 19.6 | 42.8 / 22.3 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| Stigmatization | | | | |
| Therapy start | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 49.0 / 28.6 | 45.7 / 30.5 | 47.3 / 29.4 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |
| 24 weeks | N | 34 | 37 | 71 |
| | Arithmetic mean / STD | 47.3 / 32.0 | 44.1 / 30.3 | 45.7 / 30.9 |
| | Range | 0.0 – 100.0 | 0.0 – 100.0 | 0.0 – 100.0 |

Source: Table 14.4.3.1

**Table 31: QLQ-AA/PNH scales by treatment arm at 24 weeks after start of treatment, changes from baseline (FAS)**

| Number of patients N (%) | | Eltrombopag | Placebo | Total |
|---|---|---|---|---|
| Body image | Improvement | 11 (26.8%) | 9 (20.5%) | 20 (23.5%) |
| | No change | 13 (31.7%) | 9 (20.5%) | 22 (25.9%) |
| | Deterioration | 6 (14.6%) | 8 (18.2%) | 14 (16.5%) |
| | Comparison between treatment arms | p=0.888 | | |
| Cognitive functioning | Improvement | 10 (24.4%) | 8 (18.2%) | 18 (21.2%) |
| | No change | 21 (51.2%) | 15 (34.1%) | 36 (42.4%) |
| | Deterioration | 7 (17.1%) | 8 (18.2%) | 15 (17.6%) |
| | Comparison between treatment arms | p=0.468 | | |

| Number of patients N (%) | | Eltrombopag | Placebo | Total |
|---|---|---|---|---|
| Emotional functioning | Improvement | 10 (24.4%) | 8 (18.2%) | 18 (21.2%) |
| | No change | 20 (48.8%) | 10 (22.7%) | 30 (35.3%) |
| | Deterioration | 6 (14.6%) | 8 (18.2%) | 14 (16.5%) |
| | Comparison between treatment arms | p=0.172 | | |
| Fatigue | Improvement | 11 (26.8%) | 8 (18.2%) | 19 (22.4%) |
| | No change | 17 (41.5%) | 15 (34.1%) | 32 (37.6%) |
| | Deterioration | 7 (17.1%) | 8 (18.2%) | 15 (17.6%) |
| | Comparison between treatment arms | p=0.877 | | |
| Illness intrusiveness | Improvement | 11 (26.8%) | 10 (22.7%) | 21 (24.7%) |
| | No change | 16 (39.0%) | 14 (31.8%) | 30 (35.3%) |
| | Deterioration | 7 (17.1%) | 8 (18.2%) | 15 (17.6%) |
| | Comparison between treatment arms | p=1.000 | | |
| Infections | Improvement | 17 (41.5%) | 6 (13.6%) | 23 (27.1%) |
| | No change | 11 (26.8%) | 13 (29.5%) | 24 (28.2%) |
| | Deterioration | 6 (14.6%) | 8 (18.2%) | 14 (16.5%) |
| | Comparison between treatment arms | p=0.043 | | |
| Other symptoms | Improvement | 10 (24.4%) | 7 (15.9%) | 17 (20.0%) |
| | No change | 12 (29.3%) | 19 (43.2%) | 31 (36.5%) |
| | Deterioration | 7 (17.1%) | 8 (18.2%) | 15 (17.6%) |
| | Comparison between treatment arms | p=0.108 | | |
| Fear of progression | Improvement | 5 (12.2%) | 4 (9.1%) | 9 (10.6%) |
| | No change | 19 (46.3%) | 17 (38.6%) | 36 (42.4%) |
| | Deterioration | 7 (17.1%) | 8 (18.2%) | 15 (17.6%) |
| | Comparison between treatment arms | p=1.000 | | |
| Physical functioning | Improvement | 15 (36.6%) | 16 (36.4%) | 31 (36.5%) |
| | No change | 11 (26.8%) | 6 (13.6%) | 17 (20.0%) |
| | Deterioration | 7 (17.1%) | 8 (18.2%) | 15 (17.6%) |
| | Comparison between treatment arms | p=0.855 | | |
| Role functioning | Improvement | 13 (31.7%) | 10 (22.7%) | 23 (27.1%) |
| | No change | 16 (39.0%) | 16 (36.4%) | 32 (37.6%) |
| | Deterioration | 6 (14.6%) | 8 (18.2%) | 14 (16.5%) |
| | Comparison between treatment arms | p=0.768 | | |
| Social support | Improvement | 14 (34.1%) | 9 (20.5%) | 23 (27.1%) |
| | No change | 17 (41.5%) | 15 (34.1%) | 32 (37.6%) |
| | Deterioration | 6 (14.6%) | 8 (18.2%) | 14 (16.5%) |
| | Comparison between treatment arms | p=0.539 | | |
| Stigmatization | Improvement | 9 (22.0%) | 5 (11.4%) | 14 (16.5%) |
| | No change | 19 (46.3%) | 22 (50.0%) | 41 (48.2%) |
| | Deterioration | 7 (17.1%) | 8 (18.2%) | 15 (17.6%) |

| Number of patients N (%) | Eltrombopag | Placebo | Total |
|---|---|---|---|
| Comparison between treatment arms | p=0.410 | | |

Source: Table 14.4.3.3

# 12 Safety evaluation

## 12.1 Analysis set

The SAF included all 77 patients who received treatment for ≥ 10 weeks, 41 in the placebo group and 36 in the eltrombopag group, see Section 16.2.3.

## 12.2 Extent of exposure

Treatment duration and compliance are summarized in Section 11.1 and Section 14.1.3.

## 12.3 Adverse events

### 12.3.1 Brief summary of adverse events

For this trial, only TEAEs were documented. AEs were considered to be treatment-emergent if they had started or worsened between the first study-related procedure (i.e. screening) and 30 days post the last study treatment, or after this date if the investigator felt the event was related to the IMP.

Safety data are summarized in Section 14.3. Individual patient listings of SAEs and AEs are provided in Section 16.2.10.1 and Section 16.2.10.2, respectively.

No SADRs or fatal events were reported within the first 6 months after therapy start.

Overall, 70/77 patients (90.9%) experienced a TEAE within the first 6 months of treatment. 37.7% of patients in the SAF population suffered from a TEAE assessed as related to the study medication (eltrombopag or placebo) within the first 10 weeks and 20.8% between 10 weeks and 6 months. In general, the proportion of patients with TEAEs/ADRs were in the same range for both treatment groups, although the number of events tended to be lower in the Eltrombopag Arm within the first 10 weeks (Table 35 and Table 36) and the proportion of patients with ADRs between 10 weeks and 6 months was higher in the Eltrombopag Arm (27.8% versus 14.6%), see Table 32 and Table 33.

SAEs were reported for 8/77 patients (10.4%) within the first 10 weeks and for 8/77 patients (10.4%) between 10 weeks and 6 months. These included the following:

Within the first 10 weeks (Table 40)

- Eltrombopag Arm: pyrexia, anemia, visual impairment and abdominal pain (1 patient each)
- Placebo Arm: appendicitis, meningitis, pneumonia, fatigue, hyperkalemia, syncope, tooth extraction (1 patient each)

Between 10 weeks and 6 months (Table 43)

- Eltrombopag Arm: hemolysis, myocardial infarction, condition aggravated, COVID-19 pneumonia (1 patient each)
- Placebo Arm: blood bilirubin increased, cerebral venous thrombosis, syncope, anemia, subcutaneous hematoma (1 patient each)

None of these SAEs was assessed as related to the study medication.

For number of patients with AEs and number of events starting later than 6 months of therapy please refer to Table 34 and Table 37.

Two patients in Group C experienced an SAE that was assessed as related to the study medication; one patient suffered from thrombosis and another developed pulmonary embolism. These events were expected according to the safety information. Thus, no SUSAR occurred during the course of the study.

**Table 32: Overall summary of number of patients with TEAEs reported within the first 10 weeks after therapy start (SAF)**

| Number of patients with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| AE (serious or not, related or not) | 31 | 86.1 | 39 | 95.1 | 70 | 90.9 |
| ADR (serious or not) | 14 | 38.9 | 15 | 36.6 | 29 | 37.7 |
| SAE (related or not) | 3 | 8.3 | 5 | 12.2 | 8 | 10.4 |

Source: Table 14.3.1.1

**Table 33: Overall summary of number of patients with TEAEs reported between 10 weeks and 6 months after therapy start (SAF)**

| Number of patients with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| AE (serious or not, related or not) | 30 | 83.3 | 28 | 68.3 | 58 | 75.3 |
| ADR (serious or not) | 10 | 27.8 | 6 | 14.6 | 16 | 20.8 |
| SAE (related or not) | 4 | 11.1 | 4 | 9.8 | 8 | 10.4 |

Source: Table 14.3.3.1

**Table 34: Overall summary of number of patients with TEAEs reported later than 6 months after therapy start (SAF)**

| Number of patients with at least one such event | A1 N=5 | | A2 N=29 | | B N=2 | | C N=26 | | D N=9 | | Other N=14 | | Total N=77 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| AE | 5 | 100.0 | 28 | 96.6 | 1 | 50.0 | 20 | 76.9 | 2 | 22.2 | 2 | 14.3 | 58 | 75.3 |
| ADR | 3 | 60.0 | 9 | 31.0 | 0 | 0.0 | 6 | 23.1 | 0 | 0.0 | 0 | 0.0 | 18 | 23.4 |
| SAE | 1 | 20.0 | 9 | 31.0 | 0 | 0.0 | 5 | 19.2 | 0 | 0.0 | 2 | 14.3 | 17 | 22.1 |
| SADR | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 2 | 7.7 | 0 | 0.0 | 0 | 0.0 | 2 | 2.6 |

Source: Table 14.3.5.1

**Table 35: Overall summary of TEAEs reported within the first 10 weeks after therapy start (SAF)**

| Number of events | Eltrombopag | | Placebo | | Total | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| AE (serious or not, related or not) | 188 | 100.0 | 230 | 100.0 | 418 | 100.0 |
| ADR (serious or not) | 30 | 16.0 | 50 | 21.7 | 80 | 19.1 |
| SAE (related or not) | 4 | 2.1 | 7 | 3.0 | 11 | 2.6 |

Source: Table 14.3.2.1

**Table 36: Overall summary of TEAEs reported between 10 weeks and 6 months after therapy start (SAF)**

| Number of events | Eltrombopag | | Placebo | | Total | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| AE (serious or not, related or not) | 93 | 49.5 | 87 | 37.8 | 180 | 43.1 |
| ADR (serious or not) | 18 | 9.6 | 14 | 6.1 | 32 | 7.7 |
| SAE (related or not) | 4 | 2.1 | 5 | 2.2 | 9 | 2.2 |

Source: Table 14.3.4.1

**Table 37: Overall summary of TEAEs reported later than 6 months after therapy start (SAF)**

| Number of events | A1 | | A2 | | B | | C | | D | | Other | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| AE | 24 | 100.0 | 150 | 100.0 | 4 | 100.0 | 74 | 100.0 | 2 | 100.0 | 2 | 100.0 | 256 | 100.0 |
| ADR | 3 | 12.5 | 14 | 9.3 | 0 | 0.0 | 11 | 14.9 | 0 | 0.0 | 0 | 0.0 | 28 | 10.9 |
| SAE | 4 | 16.7 | 13 | 8.7 | 0 | 0.0 | 5 | 6.8 | 0 | 0.0 | 2 | 100.0 | 24 | 9.4 |
| SADR | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 2 | 2.7 | 0 | 0.0 | 0 | 0.0 | 2 | 0.8 |

Source: Table 14.3.6.1

### 12.3.2 Analysis of adverse events

No deaths or SAEs related to the study treatment were reported in the first 6 months after therapy start. For 2 patients in Group C drug-related SAEs were reported after 6 months; 1 patient with thrombosis and 1 patient with pulmonary embolism. Another patient in Group A2 developed pyrexia while under eltrombopag treatment which was assessed as not related by the investigator but as related by the second assessment of the CPI.

A summary of TEAEs and ADRs by SOC and a summary of SAEs by SOC and PT for the different reporting periods are provided in Table 38 to Table 43.

For number of events within the first 10 weeks by SOC and PT see Tables 14.3.2.2 (TEAEs), 14.3.2.3 (ADRs) and 14.3.2.4 (SAEs).

For number of events between 10 weeks and 6 months by SOC and PT see Tables 14.3.4.2 (TEAEs), 14.3.4.3 (ADRs) and 14.3.4.4 (SAEs).

AEs reported later than 6 months after start of therapy are summarized by SOC and PT in

Section 14.3.5 (patient summaries) and Section 14.3.6 (event summaries).

**Table 38: Number of patients with TEAEs reported within the first 10 weeks after therapy start by SOC (SAF)**

| Number of patients with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Total | 31 | 86.1 | 39 | 95.1 | 70 | 90.9 |
| Gastrointestinal disorders | 19 | 52.8 | 25 | 61.0 | 44 | 57.1 |
| Nervous system disorders | 19 | 52.8 | 24 | 58.5 | 43 | 55.8 |
| General disorders and administration site conditions | 13 | 36.1 | 20 | 48.8 | 33 | 42.9 |
| Musculoskeletal and connective tissue disorders | 12 | 33.3 | 19 | 46.3 | 31 | 40.3 |
| Respiratory, thoracic and mediastinal disorders | 11 | 30.6 | 13 | 31.7 | 24 | 31.2 |
| Infections and infestations | 9 | 25.0 | 13 | 31.7 | 22 | 28.6 |
| Skin and subcutaneous tissue disorders | 8 | 22.2 | 10 | 24.4 | 18 | 23.4 |
| Vascular disorders | 8 | 22.2 | 9 | 22.0 | 17 | 22.1 |
| Investigations | 5 | 13.9 | 6 | 14.6 | 11 | 14.3 |
| Hepatobiliary disorders | 9 | 25.0 | 1 | 2.4 | 10 | 13.0 |
| Renal and urinary disorders | 4 | 11.1 | 5 | 12.2 | 9 | 11.7 |
| Ear and labyrinth disorders | 4 | 11.1 | 4 | 9.8 | 8 | 10.4 |
| Metabolism and nutrition disorders | 3 | 8.3 | 5 | 12.2 | 8 | 10.4 |
| Eye disorders | 5 | 13.9 | 1 | 2.4 | 6 | 7.8 |
| Psychiatric disorders | 2 | 5.6 | 4 | 9.8 | 6 | 7.8 |
| Cardiac disorders | 2 | 5.6 | 2 | 4.9 | 4 | 5.2 |
| Reproductive system and breast disorders | 2 | 5.6 | 2 | 4.9 | 4 | 5.2 |
| Blood and lymphatic system disorders | 1 | 2.8 | 1 | 2.4 | 2 | 2.6 |
| Injury, poisoning and procedural complications | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Surgical and medical procedures | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |

Source: Table 14.3.1.2

**Table 39: Number of patients with ADRs reported within the first 10 weeks after therapy start by SOC (SAF)**

| Number of subjects with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Total | 14 | 38.9 | 15 | 36.6 | 29 | 37.7 |
| Nervous system disorders | 5 | 13.9 | 10 | 24.4 | 15 | 19.5 |
| General disorders and administration site conditions | 3 | 8.3 | 8 | 19.5 | 11 | 14.3 |
| Gastrointestinal disorders | 6 | 16.7 | 4 | 9.8 | 10 | 13.0 |
| Investigations | 3 | 8.3 | 3 | 7.3 | 6 | 7.8 |
| Musculoskeletal and connective tissue disorders | 2 | 5.6 | 2 | 4.9 | 4 | 5.2 |
| Skin and subcutaneous tissue disorders | 1 | 2.8 | 3 | 7.3 | 4 | 5.2 |
| Vascular disorders | 1 | 2.8 | 3 | 7.3 | 4 | 5.2 |
| Renal and urinary disorders | 2 | 5.6 | 1 | 2.4 | 3 | 3.9 |
| Infections and infestations | 2 | 5.6 | 0 | 0.0 | 2 | 2.6 |
| Metabolism and nutrition disorders | 2 | 5.6 | 0 | 0.0 | 2 | 2.6 |
| Blood and lymphatic system disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Psychiatric disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |

Source: Table 14.3.1.3

**Table 40: Number of patients with SAEs reported within the first 10 weeks after therapy start by SOC and PT (SAF)**

| Number of subjects with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Total | 3 | 8.3 | 5 | 12.2 | 8 | 10.4 |
| Infections and infestations | 0 | 0.0 | 3 | 7.3 | 3 | 3.9 |
| Appendicitis | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Meningitis | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Pneumonia | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| General disorders and administration site conditions | 1 | 2.8 | 1 | 2.4 | 2 | 2.6 |
| Pyrexia | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Fatigue | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Blood and lymphatic system disorders | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Anemia | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Eye disorders | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Visual impairment | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Gastrointestinal disorders | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Abdominal pain | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Metabolism and nutrition disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Hyperkalemia | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Nervous system disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Syncope | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Surgical and medical procedures | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Tooth extraction | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |

Source: Table 14.3.1.4

**Table 41: Number of patients with TEAEs reported between 10 weeks and 6 months after therapy start by SOC (SAF)**

| Number of subjects with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Total | 30 | 83.3 | 28 | 68.3 | 58 | 75.3 |
| Gastrointestinal disorders | 11 | 30.6 | 16 | 39.0 | 27 | 35.1 |
| Skin and subcutaneous tissue disorders | 10 | 27.8 | 14 | 34.1 | 24 | 31.2 |
| Nervous system disorders | 10 | 27.8 | 8 | 19.5 | 18 | 23.4 |
| Infections and infestations | 10 | 27.8 | 6 | 14.6 | 16 | 20.8 |
| Investigations | 5 | 13.9 | 3 | 7.3 | 8 | 10.4 |
| Vascular disorders | 3 | 8.3 | 4 | 9.8 | 7 | 9.1 |

| Number of subjects with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| General disorders and administration site conditions | 4 | 11.1 | 2 | 4.9 | 6 | 7.8 |
| Musculoskeletal and connective tissue disorders | 4 | 11.1 | 2 | 4.9 | 6 | 7.8 |
| Respiratory, thoracic and mediastinal disorders | 4 | 11.1 | 2 | 4.9 | 6 | 7.8 |
| Cardiac disorders | 2 | 5.6 | 2 | 4.9 | 4 | 5.2 |
| Metabolism and nutrition disorders | 2 | 5.6 | 2 | 4.9 | 4 | 5.2 |
| Hepatobiliary disorders | 2 | 5.6 | 1 | 2.4 | 3 | 3.9 |
| Renal and urinary disorders | 1 | 2.8 | 2 | 4.9 | 3 | 3.9 |
| Reproductive system and breast disorders | 1 | 2.8 | 2 | 4.9 | 3 | 3.9 |
| Blood and lymphatic system disorders | 1 | 2.8 | 1 | 2.4 | 2 | 2.6 |
| Ear and labyrinth disorders | 0 | 0.0 | 2 | 4.9 | 2 | 2.6 |
| Surgical and medical procedures | 0 | 0.0 | 2 | 4.9 | 2 | 2.6 |
| Eye disorders | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Immune system disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Injury, poisoning and procedural complications | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Psychiatric disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |

Source: Table 14.3.3.2

**Table 42: Number of patients with ADRs reported between 10 weeks and 6 months after therapy start by SOC (SAF)**

| Number of subjects with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Total | 10 | 27.8 | 6 | 14.6 | 16 | 20.8 |
| Skin and subcutaneous tissue disorders | 4 | 11.1 | 3 | 7.3 | 7 | 9.1 |
| Gastrointestinal disorders | 4 | 11.1 | 1 | 2.4 | 5 | 6.5 |
| Investigations | 3 | 8.3 | 1 | 2.4 | 4 | 5.2 |
| Nervous system disorders | 1 | 2.8 | 3 | 7.3 | 4 | 5.2 |
| Vascular disorders | 2 | 5.6 | 1 | 2.4 | 3 | 3.9 |
| Renal and urinary disorders | 0 | 0.0 | 2 | 4.9 | 2 | 2.6 |
| Ear and labyrinth disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Respiratory, thoracic and mediastinal disorders | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |

Source: Table 14.3.3.3

**Table 43: Number of patients with SAEs reported between 10 weeks and 6 months after therapy start by SOC (SAF)**

| Number of subjects with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Total | 4 | 11.1 | 4 | 9.8 | 8 | 10.4 |
| Investigations | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Blood bilirubin increased | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Nervous system disorders | 0 | 0.0 | 2 | 4.9 | 2 | 2.6 |
| Cerebral venous thrombosis | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Syncope | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Blood and lymphatic system disorders | 1 | 2.8 | 1 | 2.4 | 2 | 2.6 |
| Hemolysis | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Anemia | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Cardiac disorders | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Myocardial infarction | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| General disorders and administration site conditions | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Condition aggravated | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Infections and infestations | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| COVID-19 pneumonia | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Injury, poisoning and procedural complications | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |
| Subcutaneous hematoma | 0 | 0.0 | 1 | 2.4 | 1 | 1.3 |

Source: Table 14.3.3.4

### 12.3.3 Listing of adverse events by patient

A by patient listing of AEs is provided in Section 16.2.10.

## 12.4 Deaths, other serious adverse events, and other significant adverse events

There were no AEs with fatal outcome reported, see Section 16.2.10. SAEs are listed in Section 16.2.10.1 and discussed in Section 12.3.2. Other significant AEs are discussed in Section 11.2.9 and Section 12.5. Three cases of death were reported. Two patients died within the follow-up period (after 53.7 weeks and 72.1 weeks). Since this was outside the reporting period for AEs, no information on the cause of death was available. Another patient died from uremia and kidney failure after 6.7 weeks. Treatment with study medication had been stopped before due to decreased ANC count.

## 12.5 Other medical events

Patients with bleeding events during the study are summarized in Table 44 and Table 45.

**Table 44: Number of patients with bleeding events within the first 6 months after therapy start (SAF)**

| Number of patients with at least one such bleeding | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| **WHO scale** | **N** | **%** | **N** | **%** | **N** | **%** |
| **Within the first 10 weeks** | | | | | | |
| 2 – Mild blood loss | 9 | 25.0 | 9 | 22.0 | 18 | 23.4 |
| 3 – Gross blood loss | 4 | 11.1 | 7 | 17.1 | 11 | 14.3 |
| 4 – Debilitating blood loss | 3 | 8.3 | 1 | 2.4 | 4 | 5.2 |
| Total | 12 | 33.3 | 12 | 29.3 | 24 | 31.2 |
| **Between 10 weeks and 6 months** | | | | | | |
| 2 – Mild blood loss | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| 3 – Gross blood loss | 3 | 8.3 | 2 | 4.9 | 5 | 6.5 |
| Total | 4 | 11.1 | 2 | 4.9 | 6 | 7.8 |

Source: Table 14.3.7.1 and Table 14.3.7.2

**Table 45: Number of patients with bleeding events after 6 months (SAF)**

| Number of patients with at least one such bleeding | A1 N=5 | | A2 N=29 | | C N=26 | | Total N=77 | |
|---|---|---|---|---|---|---|---|---|
| **WHO scale** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| 1 - Petechiae | 0 | 0.0 | 0 | 0.0 | 1 | 3.8 | 1 | 1.3 |
| 2 - Mild blood loss | 0 | 0.0 | 2 | 6.9 | 1 | 3.8 | 3 | 3.9 |
| 3 - Gross blood loss | 2 | 40.0 | 2 | 6.9 | 1 | 3.8 | 5 | 6.5 |
| Total | 2 | 40.0 | 3 | 10.3 | 2 | 7.7 | 7 | 9.1 |

Source: Table 14.3.7.3

Number of patients with anemia events during the study are provided in Table 46 and Table 47.

**Table 46: Number of patients with anemia within the first 6 months after therapy start (SAF)**

| Number of patients with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| **WHO scale** | **N** | **%** | **N** | **%** | **N** | **%** |
| **Within the first 10 weeks** | | | | | | |
| Grade 0 | 2 | 5.6 | 2 | 4.9 | 4 | 5.2 |
| Grade 1 | 13 | 36.1 | 20 | 48.8 | 33 | 42.9 |
| Grade 2 | 17 | 47.2 | 27 | 65.9 | 44 | 57.1 |
| Grade 3 | 3 | 8.3 | 11 | 26.8 | 14 | 18.2 |
| Total | 22 | 61.1 | 34 | 82.9 | 56 | 72.7 |

| Number of patients with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| **WHO scale** | **N** | **%** | **N** | **%** | **N** | **%** |
| **Between 10 weeks and 6 months** | | | | | | |
| Grade 0 | 2 | 5.6 | 4 | 9.8 | 6 | 7.8 |
| Grade 1 | 9 | 25.0 | 10 | 24.4 | 19 | 24.7 |
| Grade 2 | 13 | 36.1 | 21 | 51.2 | 34 | 44.2 |
| Grade 3 | 0 | 0.0 | 4 | 9.8 | 4 | 5.2 |
| Total | 16 | 44.4 | 25 | 61.0 | 41 | 53.2 |

Source: Table 14.3.8.1 and Table 14.3.8.2

**Table 47: Number of patients with anemia after 6 months (SAF)**

| Number of patients with at least one such event | A1 N=5 | | A2 N=29 | | C N=26 | | D N=9 | | Total N=77 | |
|---|---|---|---|---|---|---|---|---|---|---|
| **WHO scale** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| Grade 0 | 0 | 0.0 | 5 | 17.2 | 4 | 15.4 | 0 | 0.0 | 9 | 11.7 |
| Grade 1 | 2 | 40.0 | 16 | 55.2 | 9 | 34.6 | 1 | 11.1 | 29 | 37.7 |
| Grade 2 | 3 | 60.0 | 12 | 41.4 | 7 | 26.9 | 3 | 33.3 | 26 | 33.8 |
| Grade 3 | 1 | 20.0 | 2 | 6.9 | 0 | 0.0 | 0 | 0.0 | 3 | 3.9 |
| Total | 3 | 60.0 | 20 | 69.0 | 11 | 42.3 | 3 | 33.3 | 38 | 49.4 |

Source: Table 14.3.8.3

On overview of other medical events is given in Table 48 and Table 49.

**Table 48: Number of patients with other special medical events within the first 6 months after therapy start (SAF)**

| Number of patients with at least one such event | Eltrombopag N=36 | | Placebo N=41 | | Total N=77 | |
|---|---|---|---|---|---|---|
| **Type** | **N** | **%** | **N** | **%** | **N** | **%** |
| **Within the first 10 weeks** | | | | | | |
| Hemolysis/PNH symptoms | 3 | 8.3 | 1 | 2.4 | 4 | 5.2 |
| Fatigue | 2 | 5.6 | 1 | 2.4 | 3 | 3.9 |
| Hemoglobinuria | 2 | 5.6 | 1 | 2.4 | 3 | 3.9 |
| Dyspnea | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| **Between 10 weeks and 6 months** | | | | | | |
| Hemolysis/PNH symptoms | 3 | 8.3 | 0 | 0.0 | 3 | 3.9 |
| Abdominal pain | 2 | 5.6 | 0 | 0.0 | 2 | 2.6 |
| Dyspnea | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Fatigue | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |
| Hemoglobinuria | 1 | 2.8 | 0 | 0.0 | 1 | 1.3 |

Source: Table 14.3.9.1 and Table 14.3.9.2

**Table 49: Number of patients with other special medical events after 6 months (SAF)**

| Number of patients with at least one such event | A2 N=29 | | C N=26 | | Total N=77 | |
|---|---|---|---|---|---|---|
| **Type** | **N** | **%** | **N** | **%** | **N** | **%** |
| Hemolysis/PNH symptoms | 4 | 13.8 | 1 | 3.8 | 5 | 6.5 |
| Fatigue | 3 | 10.3 | 1 | 3.8 | 4 | 5.2 |
| Abdominal pain | 2 | 6.9 | 1 | 3.8 | 3 | 3.9 |
| Hemoglobinuria | 2 | 6.9 | 1 | 3.8 | 3 | 3.9 |
| Chest pain | 1 | 3.4 | 0 | 0.0 | 1 | 1.3 |
| Dysphagia | 1 | 3.4 | 0 | 0.0 | 1 | 1.3 |
| Dyspnea | 1 | 3.4 | 0 | 0.0 | 1 | 1.3 |
| Erectile dysfunction | 1 | 3.4 | 0 | 0.0 | 1 | 1.3 |

Source: Table 14.3.9.3

## 12.6 Pregnancies

One case of pregnancy was reported for a patient who initially received placebo (Group B). The pregnancy occurred during the follow-up phase more than 13 months after the patient received last study treatment.

## 12.7 Clinical laboratory evaluation

A summary of clinical laboratory data is provided in Sections 14.3.10 (blood count), 14.3.16 (bone marrow), 14.3.17 (clinical chemistry) and 14.3.18 (GPI-AP flow). Clinically significant findings in clinical chemistry are also summarized by treatment arm in Table 50.

Only a small proportion of patients (maximum 7 patients; 9.25% per parameter) showed clinically significant laboratory abnormalities. The parameters affected and the extent of the change were within the range expected for the underlying disease, AA, with accompanying PNH clones and treatment with transfusions and CSA. The most common finding, and one that became increasingly prevalent over time, was elevated creatinine levels, which is a known adverse effect of treatment with CSA. Elevated ferritin can be explained by the underlying disease in combination with transfusion-related iron intake.

**Table 50: Occurrence of clinically significant values in clinical chemistry (SAF)**

| Number of patients with at least one clinically significant value | | Eltrombopag N=36 | Placebo N=41 | Total N=77 |
|---|---|---|---|---|
| Parameter | Period | N (%) | N (%) | N (%) |
| Creatinine | Pre-study | 0 | 1 (2.4%) | 1 (1.3%) |
| | First 6 months | 3 (8.3%) | 3 (7.3%) | 6 (7.8%) |
| | After 6 months | 2 (5.6%) | 5 (12.2% | 7 (9.1%) |
| Urea | First 6 months | 0 | 2 (4.9%) | 2 (2.6%) |
| | After 6 months | 0 | 3 (7.3%) | 3 (3.9%) |
| Uric acid | After 6 months | 0 | 1 (2.4%) | 1 (1.3%) |
| Glucose | First 6 months | 1 (2.8%) | 0 | 1 (1.3%) |
| | After 6 months | 0 | 1 (2.4%) | 1 (1.3%) |
| LDH | Pre-study | 0 | 1 (2.4%) | 1 (1.3%) |
| | First 6 months | 2 (5.6%) | 0 | 2 (2.6%) |
| | After 6 months | 2 (5.6%) | 1 (2.4%) | 3 (3.9%) |
| AST | After 6 months | 1 (2.8%) | 0 | 1 (1.3%) |
| ALT | First 6 months | 0 | 1 (2.4%) | 1 (1.3%) |
| | After 6 months | 1 (2.8%) | 0 | 1 (1.3%) |
| GGT | First 6 months | 0 | 2 (4.9%) | 2 (2.6%) |
| | After 6 months | 1 (2.8%) | 0 | 1 (1.3%) |
| AP | First 6 months | 1 (2.8%) | 0 | 1 (1.3%) |
| Protein | After 6 months | 0 | 1 (2.4%) | 1 (1.3%) |
| Bilirubin | Pre-study | 0 | 1 (2.4%) | 1 (1.3%) |
| | First 6 months | 1 (2.8%) | 1 (2.4%) | 2 (2.6%) |
| Ferritin | Pre-study | 1 (2.8%) | 0 | 1 (1.3%) |
| | First 6 months | 1 (2.8%) | 1 (2.4%) | 2 (2.6%) |
| | After 6 months | 0 | 3 (7.3%) | 3 (3.9%) |

Source: Table 14.3.17.1

## 12.8 Vital signs, physical findings, and other observations related to safety

Boxplots for weight, systolic and diastolic blood pressure per treatment arm over time are provided in Section 14.3.11.

No change of weight during the treatment period was noted. There was a tendency for slight increase of both systolic and diastolic blood pressure. This was observed in both arms and was most likely due to treatment with CSA which was administered as background treatment in both arms. There was no obvious difference in systolic or diastolic blood pressure between the treatment arms. If any, the differences were minimal, and the median systolic and diastolic pressure was higher in the Placebo Arm at most observation times.

Abnormal findings in physical examination and ECG are summarized in Table 14.3.12.1 and Table 14.3.13.1, respectively.

There were no signals of differences in the number or type of abnormal ECG findings among the Eltrombopag or Placebo Arms and no increase of abnormal findings comparing the first

6 months and after 6 months. The total number of abnormal findings in the first 6 months was 14 and 13 in the Eltrombopag and the Placebo Arm, respectively, and after 6 months it was 6 and 13 in the Eltrombopag and Placebo Arm, respectively, see Table 14.3.13.1.

Findings of the ophthalmologic examination are listed in Tables 14.3.14.1 and 14.3.14.2. There were some differences in the baseline investigation, e.g. more patients with glasses / contact lenses or more lenticular changes in the Eltrombopag Arm. In further follow-up examinations, only a few patients had findings that were not already present at baseline (see Table 14.3.14.2). In the first 6 months 6 and 4 new findings were detected in the Eltrombopag and the Placebo Arm, respectively.

Abnormal findings in cytogenetics are summarized in Tables 14.3.15.1 and 14.3.15.2. It is known that a substantial proportion of patients with AA harbor clonal hematopoiesis. The findings on cytogenetic abnormalities at baseline are in the expected range of newly diagnosed patients. In follow-up examinations, there was no evidence for marked clonal evolution. The type of abnormal findings (e.g. trisomy 8, monosomy 7, mutation in PIGA or DNMTA3A) are quite common in AA, also without eltrombopag treatment. Thus, this data did not provide a signal that eltrombopag might promote clonal evolution.

By subject listings of abnormal findings in physical examination, ECG and clinical chemistry can be found in Sections 16.2.7 to 16.2.9.

### 12.9 Safety conclusions

No SADRs occurred within the first 6 months of treatment. Eltrombopag was well tolerated. There were no differences in ADRs between placebo and eltrombopag. Possible side effects of eltrombopag and the background medication with CSA are described in Sections 9.4.9.8 and 9.4.9.9. In the context of the points mentioned there, it should be noted that no bleeding after discontinuation of eltrombopag therapy, and no bone marrow fibrosis were observed in this study. There was one case of newly diagnosed cataracts in the Eltrombopag Arm within the first six months. With regard to CSA, it should be noted that there were some patients with an increase in creatinine levels, but the frequency and the grade of creatinine increase was not unusual for AA patients receiving CSA treatment.

Only three SAEs (one patient suffered from thrombosis, one developed pulmonary embolism and another presented with pyrexia) occurred that were assessed as related to the study medication and were expected according to the reference safety information. Thus, no additional risks or new toxicities for eltrombopag treatment in the dosing regimen applied in this study with concomitant CSA background medication had emerged during the course of the study.

## 13 Discussion and overall conclusions

The median age of patients was 53 years (IQR 35-65 years); 47.1% were female; and 57.6% required transfusions within 12 weeks prior to enrollment. The median (IQR) baseline platelet, neutrophil and hemoglobin concentrations were 22x10⁹/L (14-29x10⁹/L), 0.98x10⁹/L (0.64-1.29x10⁹/L), and 9.0 g/dL (8.2-9.8 g/dL), respectively. Patient characteristics in the two arms were well balanced. All 85 randomized patients were tracked and analyzed. Ten patients discontinued before the 24-week evaluation (4 in the Placebo Arm and 6 in the Eltrombopag Arm) due to progression (3 in the Placebo Arm and 1 in the Eltrombopag Arm), AE (1 in the Eltrombopag Arm), withdrawal of informed consent (1 in the Eltrombopag Arm), and other

reasons (4 patients).

In the per-protocol set (PPS), the ORR, including PR and CR, after 24 weeks was significantly higher in the Eltrombopag Arm (71.4%; 25/35 patients; 95% CI 54.8; 83.8) than in the Placebo Arm (42.5%; 17/40 patients; 95% CI 28.5; 57.8; p = 0.011, Fisher's exact test; OR 3.325; 95% lower limit for OR 1.354). At 24 weeks, the proportion of patients with CR was 11.4% (4/35 patients; 95% CI 3.9; 26.5) in the Eltrombopag Arm and 5.0% (2/40 patients) in the Placebo Arm. Older age (>60 years) did not significantly impact the primary outcome. However, patients with transfusion-dependent MAA had a significantly lower chance of reaching the primary endpoint (p=0.007; OR 0.18; 95% CI 0.05; 0.63).

In the full analysis set (FAS), the ORR after 12 weeks was 48.8% (20/41 patients; 95% CI 34.3; 63.5) in the Eltrombopag Group and 25% (11/44 patients; 95% CI 14.4; 39.6) in the Placebo Group (p = 0.020; OR 2.821; 95% lower limit for OR 1.202).

After evaluating the response at Week 24 and unblinding, patients in the Placebo Group without CR received eltrombopag starting at week 25 (n=38, FAS) (Group A). This group achieved an ORR of 73.5% at 48 weeks (25 of 34 patients with assessment; 14 PR, 11 CR). Thus, adding eltrombopag to the placebo group increased both the ORR and the strength of response. At Week 24, the ORR was 42.5%, and at Week 48, it had increased to 73.5%. At Week 24, there were 23 NR, 15 PR, and 2 CR; at week 48, there were 9 NR, 14 PR, and 11 CR, and 4 were not assessed.

Despite this improvement, the cumulative incidence of ORR was superior in the group of patients who had been initially randomized to eltrombopag (HR 1.66; p=0.049), with a lower incidence of ORR in older patients (>60 years) and transfusion dependence (HR 0.41; p=0.016).

Overall, 70 out of 77 patients experienced a TEAE during the first 10 weeks of treatment, and 58 out of 77 patients experienced an event between Weeks 10 and 24 (until Week 10: 95.1% and 86.1% in the Placebo and Eltrombopag Arms, respectively; Week 10 to Week 24: 68.3% and 83.3% in the Placebo and Eltrombopag Arms, respectively). SAEs were reported by 8/77 patients (10.4%) within the first 10 weeks and by 8/77 patients (10.4%) between Weeks 10 and 24 (9.8% and 11.1% in the Placebo and Eltrombopag Arms, respectively). Only 3 SAEs (deep vein thrombosis, pulmonary embolism and pyrexia) occurred that were assessed as related to the study medication.

**Conclusions:**

Adding eltrombopag to CSA treatment for patients with untreated MAA significantly improved trilineage hematologic response by Week 24. The addition of eltrombopag in patients with MAA without CR after 24 weeks of single-agent CSA treatment also improved the trilineage hematologic response rate. Treatment with eltrombopag was well tolerated, and no new safety concerns were identified in patients with MAA. Eltrombopag combined with standard CSA therapy should be the preferred initial treatment for patients with MAA and could become the new standard of care for MAA patients, administered orally on an outpatient basis.

# 14 Tables, figures and graphs

# 15 References

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# 16 Appendices

## 16.1 Study information

### 16.1.1 Protocol and protocol amendments

### 16.1.2 Sample case report form

Provided in the TMF.

### 16.1.3 List of IECs or IRBs - representative written information for patient and sample consent forms

Provided in the TMF.

### 16.1.4 List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

Please refer to Section 6. More detailed information including CVs and training experience of the investigators is provided in the TMF.

### 16.1.5 Signatures of principal or coordinating investigator(s) or sponsor´s responsible medical officer, depending on the regulatory authority's requirement

See page 2 of this CSR.

### 16.1.6 Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used

Provided in the TMF.

### 16.1.7 Randomization scheme and codes (patient identification and treatment assigned)

For patient identification and assignment to treatment arms and groups please refer to Section 16.2.3.1.

### 16.1.8 Audit certificates

Not applicable.

### 16.1.9 Documentation of statistical methods

SAP version 1.0, dated 08 Jan 2025.

Deviations from the SAP:

- SAF was redefined as the subpopulation of patients who had received at least 10 weeks of study treatment (SAP: 10 weeks of eltrombopag treatment). Otherwise, observations in the Placebo Arm would have been omitted.

- Trilineage response was based on investigator assessment instead of calculated response assessment. In case of differences between calculated and investigator assessment, all results were checked and the final result was entered as investigator assessment. Thus, the investigator assessment gave the correct assessment.
- Conditions for relapse were checked without a second measurement of blood count. These were not available in the eCRF.
- Relapse rates were only calculated for patients with at least one single or trilineage response.
- In the study protocol, relapse was to be demonstrated for a minimum of two times over a period of 2 weeks. The calculation of relapse referred only to one measurement, since second measurements were not documented in the eCRF.
- The definition of date of relapse was clarified and specified as earliest of one of the following events:
    - Platelet count < 70 G/L and ANC < 1.2 G/L (criteria for MAA)
    - Either platelet count < 70 G/L or ANC < 1.2 G/L and reticulocytes < 60 G/L (criteria for MAA)
    - Any platelet transfusion within the last 4 weeks before evaluation (as evaluated by the investigator and documented at time of next visit)
    - Any pRBC transfusion within the last 6 weeks before evaluation (as evaluated by the investigator and documented at time of next visit)
    - Platelet count below baseline platelet count in case of platelet response
    - Neutrophil count below baseline neutrophil count in case of neutrophil response
    - HgB value below baseline HgB value in case of erythroid response
- Additionally, a post-hoc analysis with modified relapse criteria was performed. For the post hoc analysis, relapse from **first** trilineage response was defined as no longer meeting criteria for at least PR (i.e. patients must have received at least PR – and the next assessment which did no longer fulfill criteria for at least PR was considered as relapse (modified criteria) and the visit date was the date of relapse)
- The calculation of time to treatment failure was not consistent with the failure definition in the SAP. “Earliest date of documented non-response (not followed by response)” was replaced by “date of visit Va (in case of non-response at Va) or date of last treatment date (in case of missing date of Va)”, thus the definition reads:
  FFS was defined as survival with trilineage hematological response, i.e. time to treatment failure was calculated as date of death from any cause or date of visit Va (in case of non-response at Va) or date of last treatment (in case of missing date of Va) or date of relapse or date of documented disease progression to MDS or AML or start date of IST or stem cell transplantation whichever occurred first – date of therapy start.

### 16.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures if used

Not applicable for this study.

### 16.1.11 Publications based on the study

None.

### 16.1.12 Important publications referenced in the report

Not applicable.

## 16.2 Patient data listings

## 16.3 Narratives

Not applicable.