Sponsor: Sanofi **Drug substance:** Caplacizumab	**Study Identifiers:** NCT02553317; EudraCT 2015-001098-42 **Study code:** ALX0681-C301
Title of the study: A Phase III double-blind, randomized, parallel group, multicenter placebo-controlled trial to study the efficacy and safety of caplacizumab in patients with acquired thrombotic thrombocytopenic purpura	
Study centers: Subjects were enrolled in 55 study centers in 15 countries: Australia (3 centers), Austria (1 center), Belgium (4 centers), Canada (4 centers), Czech Republic (2 centers), France (6 centers), Hungary (2 centers), Israel (4 centers), Italy (5 centers), The Netherlands (1 center), Spain (6 centers), Switzerland (1 center), Turkey (3 centers), United Kingdom (3 centers) and the United States of America (10 centers)	
Study period: Date first participant enrolled: 19/Nov/2015 Date last participant completed: 16/Aug/2017 Study Status: Completed	
Phase of development: Phase III	
Objectives: • Primary Objective: - To evaluate efficacy of caplacizumab in more rapidly restoring normal platelet counts as measure of prevention of further microvascular thrombosis • Secondary Objectives: - to evaluate the effect of study drug on a composite endpoint consisting of thrombotic thrombocytopenic purpura (TTP)-related mortality, recurrence of TTP and major thromboembolic events during study drug treatment - to evaluate the effect of study drug on prevention of recurrence of TTP over the entire study period - to evaluate the effect of study drug on refractoriness to treatment - to evaluate the effect of study drug on biomarkers of organ damage: lactate dehydrogenase (LDH), cardiac troponin I (cTnI), and serum creatinine - to evaluate the effect of study drug on plasma exchange (PE) parameters (days of PE and volume), days in intensive care unit (ICU), days in hospital - adverse events (AEs) - pharmacodynamic (PD) markers: von Willebrand factor antigen (vWF:Ag), coagulation factor VIII clotting activity (FVIII:C), ristocetin cofactor activity (RICO) - pharmacokinetic (PK) parameters - immunogenicity (anti-drug antibodies [ADA])	

Methodology:

This was a Phase III, randomized, double-blind, placebo-controlled, study to evaluate the efficacy and safety of caplacizumab when administered in addition to standard of care treatment in subjects with an acute episode of acquired TTP. The study evaluated the efficacy of caplacizumab in more rapidly restoring normal platelet counts. In addition, the effect of treatment with caplacizumab on a composite endpoint of TTP-related mortality, recurrence of TTP and major thromboembolic events during study drug treatment and on endpoints assessing recurrence of TTP during the Overall Study Period, refractory TTP and time to normalization of organ damage marker levels, were evaluated.

After confirmation of eligibility to study participation and after the start of PE treatment*, subjects were randomized in a ratio of 1:1 to receive caplacizumab or placebo in addition to standard of care therapy. Randomization was stratified by severity of neurological involvement (Glasgow coma scale [GCS]).

Number of participants:

The planned sample size was approximately 132 adult subjects in 2 arms, randomized in a 1:1 ratio and stratified by severity of neurological involvement prior to randomization (GCS score ≤ 12 versus GCS score = 13 - 15).

A total of 145 subjects (72 subjects to caplacizumab and 73 subjects to placebo) were enrolled (i.e., randomized) in the study.

Diagnosis and criteria for inclusion:

- Adult male or female ≥ 18 years of age at the time of signing the informed consent form (ICF)
- Clinical diagnosis of acquired TTP (initial or recurrent), which included thrombocytopenia and microscopic evidence of red blood cell fragmentation (e.g., schistocytes)
- Required initiation of daily PE treatment and had received 1 PE treatment prior to randomization

Study products:

Caplacizumab 10 mg – lyophilized powder for solution for injection:

- Presented in ISO 2R glass vial with FluroTec® Butyl stopper filled with lyophilisate containing 12.5 mg caplacizumab and excipients (see below).

- Active substance: caplacizumab (anti-vWF Nanobody).

- Activity: caplacizumab is directed towards the A1 domain of vWF and specifically inhibits the interaction of (ultra-large)vWF ([UL]vWF) with the platelet Glycoprotein Ib (GPIb) receptor glycoprotein, thereby preventing (UL)vWF-mediated platelet aggregation.

- Strength: One vial contained 12.5 mg of caplacizumab. This comprised an overfill to compensate for a potential loss of up to 2.5 mg of caplacizumab during reconstitution and liquid transfer. The drug product is reconstituted with 1 mL of WFI using the supplied kit components to allow for administration of 10 mg caplacizumab.

- Excipients: 0.21 mg citric acid, 5.58 mg trisodium citrate dihydrate, 70 mg sucrose, 0.11 mg polysorbate 80 per vial (pH 6.5 +/- 0.5).

- Dosage form: powder for solution for injection; reconstitution with WFI yields solution for injection.

- Route of administration: i.v. (first dose and prior to the first PE done after a first exacerbation or relapse), s.c. (all subsequent doses).

Placebo - lyophilized powder for solution for injection: - Active substance: not applicable, the composition of placebo is the same as that of active Investigational Medicinal Product (IMP), without the active ingredient. - Activity, strength: not applicable. - Excipients: 0.21 mg citric acid, 5.58 mg trisodium citrate dihydrate, 70 mg sucrose, 0.11 mg polysorbate 80 per vial (pH 6.5 +/- 0.5). - Dosage form: powder for solution for injection; reconstitution with WFI yields solution for injection. - Route of administration: i.v. (first dose and prior to the first PE done after a first exacerbation or relapse), s.c. (all subsequent doses).
Study duration: The anticipated study duration per subject ranged from 2 to 6 months. • Screening period: From signing of ICF until randomization • Study drug treatment period: Covering daily PE period (variable duration) and 30-days post-daily PE period • Treatment extension period: 7-day extensions with maximum of 28 days, i.e., 4 x 7 days • Open-label: In case an exacerbation during the 30 day treatment period or a relapse during the treatment extension period occurred (first exacerbation or relapse), subjects were to receive open label caplacizumab together with re-initiation of daily PE and optimized immunosuppressive treatment. Caplacizumab treatment schedule and visit schedule were the same as for the initial study drug treatment period (covering daily PE [variable duration] and 30-day post-daily PE period) and the possible treatment extension period. • Follow-up period of 4 weeks: Follow up visits were to be held 7 and 28 days after the last day of study drug administration.

Criteria for evaluation:

Primary:

Time to platelet count response defined as initial platelet count ≥ 150 × 109/L with subsequent stop of daily PE within 5 days.

Key secondary endpoints

The key secondary endpoints are hierarchically ordered as listed below:

1. Proportion of subjects with TTP-related death, a recurrence of TTP, or at least one treatment-emergent major thromboembolic event (e.g., myocardial infarction, cerebrovascular accident, pulmonary embolism or deep venous thrombosis [DVT]) during the study drug treatment period (including extensions).

2. Proportion of subjects with a recurrence of TTP in the Overall Study Period (including 4-week FU period).

3. Proportion of subjects with refractory TTP, defined as absence of platelet count doubling after 4 days of standard treatment, and LDH > upper limit of normal (ULN).

4. Time to normalization of all 3 of the following organ damage marker levels:

- Time to LDH ≤ 1 x ULN, and cTnI ≤ 1 x ULN, and serum creatinine ≤ 1 x ULN

Other secondary endpoints

・Proportion of subjects with recurrences of TTP as well as the number of such events during study drug treatment (including extensions) and after end of study drug treatment

・Proportion of subjects with treatment-emergent clinically significant TTP-related events, as well as the number of such events in the Overall Study Period (including 4-week FU period)

・Area under the curve (AUC) of platelet count until Day 5, truncated at 150×109/L if platelet count is 150×109/L or above

・Mortality rate during 4 time periods: initial daily PE period, full study drug treatment period, FU period (of 4 weeks after stop of study treatment) and Overall Study Period

・Organ damage markers: Time to LDH ≤ 1 x ULN

・Organ damage markers: Time to cTnI ≤ 1 x ULN

・Organ damage markers: Time to serum creatinine ≤ 1 x ULN

・Proportion of subjects with increases in organ damage markers (cTnI and serum creatinine) above 1 x ULN in 4 time periods: initial daily PE period, full study drug treatment period, FU period (of 4 weeks after stop of study treatment) and Overall Study Period

・Proportion of subjects with neurological symptoms based on neurological assessment on Day 1, 2, 3, 4, 5 and Weeks 1 and 5 of the 30-day post-daily PE treatment period, and the first and final FU visit

・Change from baseline in SMMSE total score on Days 1, 2, 3, 4, 5 and Weeks 1 and 5 of the 30-day post-daily PE treatment period, and the first and final FU visit

・Proportion of subjects with evidence of cardiac ischemia and/or arrhythmia/conduction abnormalities on Days 1, 2, 3, and 4 and Weeks 1 and 5 of the 30-day post-daily PE treatment period, and the first and final FU visit

・Proportion of subjects who have a platelet count ≥ 150 × 109/L on Day 1, 2, 3, 4, 5 and Day 10 and end of study drug treatment (i.e., last weekly visit during the study drug treatment period)

・Time to stop of daily PE

・Bleeding events (bleeding TEAEs)

・Proportion of subjects with at least one treatment-emergent thromboembolic event (based on the Standardized MedDRA Query [SMQ] Embolic and thrombotic events [arterial, venous, and vessel type unspecified and mixed arterial and venous]).

・(S)AEs

・PE parameters: number of days and total volume (absolute and normalized) in 2 time periods: initial daily PE period and full study drug treatment period

・Number of days in ICU and in hospital in 4 time periods: initial daily PE period, full study drug treatment period, in the FU period (of 4 weeks after stop of study treatment) and Overall Study Period

・PD parameters: vWF:Ag, FVIII:C, RICO

・PK parameters

・Immunogenicity (ADA)

Statistical methods:

Randomization:
Subjects were randomized to one of the 2 arms in a 1:1 ratio. Randomization was stratified by severity of neurological involvement (GCS ≤ 12 vs. GCS = 13-15). Stratification was foreseen to ensure balanced treatment arms for the secondary endpoints related to neurological involvement and not for the primary endpoint, for which the stratification parameter is not known to be relevant.
Analysis of primary endpoint:
Time to platelet count response in the caplacizumab arm and placebo arm was compared by conducting a two-sided stratified Log-rank test based on a Kaplan-Meier (KM) analysis, with severity of neurological involvement as stratification factor (according to the GCS, stratification factor used in randomization: ≤12 / 13-15). The resulting p-value was compared with a significance level of 5%.
Only data from the double blind daily PE period up to the cut-off point were used for the analysis of the primary endpoint. The data cut-off point was defined by whichever occurred first, i.e.,:
• 45 days of daily PE after the start of study drug

• the stop of daily PE

• the stop of study drug treatment.

Time to platelet count response was measured from the time of the first i.v. loading dose of study drug after randomization. In the KM analysis, an observation was censored if the defined time interval of 45 days after first administration of study drug was not met, due to any cause (e.g., endpoint not being reached within this time interval or subject lost to follow-up).

Analysis of secondary endpoints:

Key secondary endpoints

Confirmatory hypothesis testing was conducted for the key secondary endpoints. In order to control the rate of false positive conclusions with a family-wise error rate of 5%, a fixed sequence approach was applied. The key secondary endpoints were hierarchically ordered. This allowed statistical testing for these endpoints at the same nominal significance level of 5% without adjustment, as long as the tests occurred in the pre-defined sequential order, and given that all null hypotheses to be tested for endpoints with a higher rank (including the primary endpoint) were rejected. As soon as a test was not statistically significant for a certain endpoint, i.e. as soon as the sequence broke, no confirmatory testing was to be done for remaining endpoints lower in the ranking. Statistical comparison between the two treatment arms for the key secondary endpoints was done by means of the following planned analyses (in hierarchical order):

1. Proportion of subjects with TTP-related death, a recurrence of TTP, or at least one treatment-emergent major thromboembolic event (e.g., cerebrovascular accident or myocardial infarction) during the study drug treatment period (including extensions): Cochran-Mantel-Haenszel test with adjustment for severity of neurological involvement (stratification factor used in randomization). For both treatment groups, only events that occurred prior to a switch to open-label caplacizumab were evaluated for this analysis.

2. Proportion of subjects with a recurrence of TTP in the Overall Study Period (including 4-week FU period): Cochran-Mantel-Haenszel test with adjustment for severity of neurological involvement (stratification factor used in randomization). Only events that occurred prior to a switch to open-label caplacizumab were evaluated for this analysis.

3. Proportion of subjects with refractory TTP, defined as absence of platelet count doubling after 4 days of standard treatment, and LDH > ULN: Cochran-Mantel-Haenszel test with adjustment for severity of neurological involvement (stratification factor used in randomization).

4. Time to normalization of all three organ damage marker levels: stratified Log-rank test based on a KM analysis with adjustment for severity of neurological involvement and for an additional factor defining whether the subject had abnormal values at Baseline for LDH only (not for cTnI or for serum creatinine) or not. Subjects who had switched from placebo to open label caplacizumab before having reached the endpoint were censored at time of switch.

Other secondary endpoints

All other endpoints were summarized using standard statistics (such as number of observations, means, standard deviations, and proportions, as appropriate) or KM analysis.

Summary results:

In total, 145 subjects were randomized (i.e., the ITT Population), 72 to caplacizumab and 73 to placebo. 71 subjects in the caplacizumab group and 73 in the placebo group received at least one dose of study drug and were included in the Safety Population and in the mITT population. One subject randomized to caplacizumab withdrew consent prior to first dosing.

Subject demographics were as expected for a population with acquired TTP. Baseline disease characteristics were generally balanced between treatment groups except for previous TTP episodes, disease severity, ADAMTS13 activity, and levels of the organ damage markers cTnI and LDH, which disfavored the caplacizumab group. Specifically, compared to the placebo group, fewer subjects in the caplacizumab group were enrolled with a recurrent episode and more were characterized as having very severe disease at study inclusion. Also, the proportion of subjects with ADAMTS13 activity levels below 10% was lower in the caplacizumab group compared to the placebo group. Median cTnI and LDH levels were higher in the caplacizumab group compared to the placebo group.

Efficacy Results

Primary endpoint

The study's primary endpoint, time to platelet count response (defined as initial platelet count $\geqslant 150\times109$/L with subsequent stop of daily PE within 5 days), was met with a statistically significant reduction in the double blind (DB) caplacizumab group compared to the DB placebo group based on a KM analysis and a stratified log-rank test (p = 0.01). This was confirmed by a hazard (or platelet count normalization rate) ratio (95% confidence interval [CI]) for the DB caplacizumab group versus the DB placebo group of 1.55 (1.10, 2.20) based on a Cox proportional hazards model meaning that subjects treated with caplacizumab were 1.55 times more likely to achieve platelet count response at any given time point.

Key secondary endpoints

During the DB Treatment Period, treatment with caplacizumab resulted in a 74% reduction in the percentage of subjects with TTP-related death, a recurrence of TTP, or at least one treatment-emergent major thromboembolic event compared to treatment with placebo (p <0.0001).

• No subjects in the DB caplacizumab group compared to 3 subjects (4.1%) in the DB placebo group died of a TTP-related cause during the DB Study Drug Treatment Period.

• Recurrence of TTP (exacerbation) was reported in 3 subjects (4.2%) in the DB caplacizumab group and in 28 subjects (38.4%) in the DB placebo group during the DB Study Drug Treatment Period.

• Treatment-emergent major thromboembolic events occurred in 6 subjects (8.5%) in the DB caplacizumab group and 6 subjects (8.2%) in the DB placebo group during the DB Treatment Period. The most frequently adjudicated treatment-emergent major thromboembolic events were events related to deep venous thrombosis (catheter-associated) (DB caplacizumab group: 3 subjects [4.2%]; DB placebo group: 2 subjects [2.7%]) and cerebrovascular accidents (DB caplacizumab group: 2 [2.8%]; DB placebo group: 3 subjects [4.1%]). All other treatment-emergent major thromboembolic events were reported in no more than 1 subject per treatment group.

The prevention of disease recurrences by caplacizumab was sustained during the Overall Study Period, during which recurrences of TTP (exacerbations or relapses) were reported in 12.7% of subjects in the DB caplacizumab group and in 38.4% of subjects in the DB placebo group (p < 0.001), a 67% reduction. In all 6 subjects in the DB caplacizumab group who experienced a recurrence of TTP (i.e., a relapse) during the Follow-up Period, the ADAMTS13 activity level was <10% at the end of the study drug treatment, suggesting the underlying disease was still active at the time study drug was stopped.

Overall, 70% of subjects achieved resolution of the presenting episode of TTP after treatment with caplacizumab for the duration of PE and the 30 days thereafter. For most of the subjects with evidence of ongoing disease activity at the end of the 30-day post-daily PE Period, extension of treatment with caplacizumab for up to 4 weeks accompanied by optimization of immunosuppression resulted in resolution of the presenting episode of aTTP. In a small subset of subjects (approximately 5%) with evidence of ongoing disease activity at the end of the 30-day post-daily PE Period, immunosuppression may need to be further optimized. In a real world setting, to protect such patients from relapse of TTP, treatment with caplacizumab should therefore be extended until the presenting episode is resolved.

Refractoriness to therapy, defined as absence of platelet count doubling after 4 days of standard treatment with LDH > ULN, was seen in none of the subjects in the DB caplacizumab group and 3 subjects (4.2%) in the DB placebo group during the DB Treatment Period. This difference did not reach statistical significance (p = 0.06) due to the overall low number of subjects meeting this strict definition of refractoriness.

A KM analysis showed a trend towards faster normalization of the organ damage markers (LDH, cTnI and serum creatinine) in subjects treated with caplacizumab compared to subjects treated with placebo. When considering the 3 organ damage markers separately, median time to normalization of each of the 3 organ damage markers was numerically faster in the DB caplacizumab group compared to the DB placebo group.

During the DB daily PE Period, 31 subjects (43.7%) in the DB caplacizumab group and 34 subjects (46.6%) in the DB placebo group had elevated cTnI levels. For 2 subjects in the placebo group, myocardial infarction was reported as AE at the time of the peak in cTnI levels in this period. During the DB post-daily PE Period, 10 subjects (15.4%) in the DB caplacizumab group and 16 subjects (25.0%) in the DB placebo group had elevated cTnI levels. For 1 of these subjects in the caplacizumab group and 1 subject in the placebo group, myocardial infarction was reported as AE at the time of the peak in cTnI levels in this period. During the FU Period, elevated cTnI levels were observed for 2 subjects (3.0%) in the DB caplacizumab group and 2 subjects (5.1%) in the DB placebo group. For 1 of these subjects with elevated cTnI in the caplacizumab group and 1 subject with elevated cTnI in the placebo group, myocardial infarction was reported as AE starting during the treatment period and ongoing at start of the FU Period (also see above).

During the DB daily PE Period, 11 subjects (15.5%) in the DB caplacizumab group and 18 subjects (24.7%) in the DB placebo group had elevated serum creatinine levels. During the DB post-daily PE Period, 12 subjects (18.5%) in the DB caplacizumab group and 10 subjects (15.6%) in the DB placebo group had elevated serum creatinine levels. During the FU Period, elevated

serum creatinine levels were observed for 2 subjects (3.0%) and 1 subject (2.6%), respectively. None of these subjects required treatment with dialysis.

Other secondary endpoints

The majority of subjects reached platelet count ⩾ 150x109/L by Day 4 of treatment, with more subjects reaching this threshold in the DB caplacizumab group compared to the DB placebo group at this time point (75.8% versus 56.1%, respectively).

Treatment-emergent clinically significant TTP-related events (as indicated by the Investigator) were reported for 36.1% of subjects in the caplacizumab group and for 60.3% of subjects in the placebo group during the Overall Study Period.

At Baseline, 11 subjects (16.9%) in the DB caplacizumab group and 14 subjects (22.6%) in the DB placebo group had neurological symptoms. The number of subjects with neurological symptoms decreased during the daily PE Period in both treatment groups and was 3 (4.6%) in the DB caplacizumab group and 7 (11.3%) in the DB placebo group on the first day after stop of daily PE. By the end of the 30-day post-daily PE period, the number of subjects with neurological symptoms had further decreased to 2 in both treatment groups and was 1 and 2 subjects, respectively at the Day 28 FU visit.

At Baseline, median (min; max) SMMSE was 28 (0; 30) in the DB caplacizumab group and 27 (0; 30) in the DB placebo group. During the treatment period, SMMSE scores increased (i.e., improved) in both treatment groups and were 30 (7; 30) in the DB caplacizumab group and 29 (0; 30) in the DB placebo group on Day 5 of daily PE and 30 (7; 30) and 30 (19; 30), respectively, at the end of the 30-day post-daily PE period. At the Day 28 FU visit, median (min; max) SMMSE was 30 (23; 30) in the DB caplacizumab group and 30 (21; 30) in the DB placebo group.

Treatment with caplacizumab resulted in a 38% reduction in the mean number of days of plasma exchange (reduction of 3.6 days) during the Overall Study Drug Treatment Period.

Treatment with caplacizumab resulted in a 65% reduction in the mean length of ICU stay (reduction of 6.3 days) and a 31% reduction in the mean length of hospitalization (reduction of 4.5 days) during the Overall Study Drug Treatment Period.

Pharmacodynamic Results

In the caplacizumab group, mean RICO activity was suppressed to <20% (neutralization of target) throughout the Overall Study Drug Treatment Period. PD parameters mean vWF:Ag levels and mean FVIII:C activity decreased during the first days of dosing (Daily PE Period), remained low at subsequent time points during the Overall Study Drug Treatment Period, and were lower than in the placebo group throughout the Overall Study Drug Treatment Period.

After treatment with caplacizumab was stopped, mean RICO activity recovered and mean vWF:Ag levels, and mean FVIII:C levels increased and were similar to levels in the placebo group during the FU Period.

Pharmacokinetic Results

Mean plasma concentrations of caplacizumab ranged between 441 ng/mL and 529 ng/mL during the Post-daily PE Period. In general, as of Day 2 of treatment with caplacizumab, all subjects with available data had RICO activity levels below 20% and this persisted throughout the Study Drug Treatment Period, which indicates that the target drug concentrations were attained and could be maintained in all subjects treated with caplacizumab.

The dosing regimen used in this study (10 mg daily) is considered adequate for reaching the desired RICO suppression and consequently, suppression of the platelet-binding capacity of (UL)vWF in TTP patients.

Immunogenicity Results

Pre-existing antibodies (pre-Abs) were detected at a similar prevalence in both caplacizumab treated-subjects (56.7%, 55/97) and in placebo-treated subjects (DB Period; 63.0%, 46/73). In this study, drug-induced TE ADA responses were noted in 3.1% (3/97) of the caplacizumab-treated subjects and in 1.4% (1/73) of the placebo treated subjects. Using the alternative and functional NAb assay, TE NAb were detected in 4.1% (4/97) and 2.1% (2/97), respectively, of the subjects treated with caplacizumab. In subjects treated placebo (DB period), 1.4% (1/73) and 0% (0/73) tested positive for TE NAb using the alternative and functional assay, respectively.

On average, observed drug concentrations were lower in subjects with pre-Ab compared to subjects without pre-Ab. No influence of pre-Ab on PD (RICO and vWF:Ag) and clinical efficacy (time to platelet count response) was found.

Safety Results

The median (min; max) duration of exposure to study drug was 35 (1; 65) days for the DB caplacizumab group and 23 (2; 66) days for the DB placebo group during the DB treatment period. During the Open-label (OL) Treatment Period, the median (min; max) duration of OL caplacizumab treatment was 36.5 (3; 65) days. The shorter median duration of exposure in subjects randomized to placebo is due to the switch to OL caplacizumab treatment upon recurrence.

During the Overall Study Period, 69 subjects (97.2%) in the DB caplacizumab group and 71 subjects (97.3%) in the DB placebo group were reported with at least one TEAE. In the OL caplacizumab group, 25 subjects (89.3%) were reported with at least one TEAE.

There were 4 deaths during the study, 3 subjects died during the Overall Study Drug Treatment Period (all in the placebo group) and 1 subject in the caplacizumab group died during the Follow-up Period when the subject was off active treatment (the event was assessed by the Investigator as not related to study drug treatment).

During the Overall Study Period, SAEs were reported in 28 subjects (39.4%) in the DB caplacizumab group and 39 subjects (53.4%) in the DB placebo group. Seven subjects (25.0%) in the OL caplacizumab group were reported with at least one SAE. Per protocol, TTP recurrences had to be reported as SAEs. The most frequently reported SAE was TTP, which was reported in less subjects (9 subjects [12.7%]) in the DB caplacizumab group compared with the DB placebo group (29 subjects [39.7%]).

SAEs considered at least possibly related to study drug by the Investigator were reported in 10 subjects (14.1%) in the DB caplacizumab group and 4 subjects (5.5%) in the DB placebo group in the Overall Study Period. The most common treatment-related SAE in the DB caplacizumab group was epistaxis (4 subjects [5.6%]).

Five subjects (7.0%) in the DB caplacizumab group and 9 subjects (12.3%) in the DB placebo group were reported with a TEAE leading to study drug discontinuation. All TEAEs leading to study drug discontinuation were reported in no more than 1 subject per treatment group except for the preferred term TTP which led to study drug discontinuation in 1 subject [1.4%] in the DB caplacizumab group and 2 subjects [2.7%] in the DB placebo group. One subject (3.6%) in the OL caplacizumab group was reported with a TEAE leading to study drug discontinuation. This concerned an event of TTP recurrence, which, per protocol, required study drug discontinuation.

The System Organ Classes (SOCs) with the most commonly reported TEAEs in the Overall Study Period were General disorders and administration site reactions (DB caplacizumab group: 37 subjects [52.1%]; DB placebo group: 36 subjects [49.3%]), Gastrointestinal disorders (DB caplacizumab group: 36 subjects [50.7%]; DB placebo group: 27 subjects [37%]), and Nervous system disorders (DB caplacizumab group: 32 subjects [45.1%]; DB placebo group: 27 subjects [37.0%]).

By preferred term (PT), the TEAEs most frequently reported during the Overall Study Period were TTP (DB caplacizumab group: 9 subjects [12.7%]; DB placebo group: 29 subjects [39.7%]), epistaxis (DB caplacizumab group: 23 subjects [32.4%]; DB placebo group: 2 subjects [2.7%]), and headache (DB caplacizumab group: 16 subjects [22.5%]; DB placebo group: 6 subjects [8.2%]). Frequencies of TEAEs of epistaxis and headache in the caplacizumab group tended to be higher during the post-daily PE period (epistaxis: 15 subjects [23.1%]; headache: 11 subjects [16.9%]) than during the daily PE period (epistaxis: 9 subjects [12.7%]; headache: 3 subjects [4.2%]).

The type of TEAEs in the OL caplacizumab group was consistent with those in the DB caplacizumab group.

TEAEs were mild in severity for the majority of the subjects (DB caplacizumab group: 28 subjects [39.4%]; DB placebo group: 27 subjects [37%]). Moderate TEAEs were reported with higher incidence in the DB caplacizumab (26 subjects [36.6%]) compared with the DB placebo (20 subjects [27.4%]) group. Severe TEAEs were reported more frequently in the DB placebo (24 subjects [32.9%]) compared with the DB caplacizumab (15 subjects [21.1%]) group.

The most frequently reported treatment-related TEAEs were epistaxis (DB caplacizumab group: 17 subjects [23.9%]; DB placebo group: 1 subject [1.4%]), gingival bleeding (DB caplacizumab group: 8 subjects [11.3%]; DB placebo group: 0), and contusion (DB caplacizumab group: 5 subjects [7%]; DB placebo group: 3 subjects [4.1%]). In the OL caplacizumab group, 20 subjects (71.4%) were reported with a TEAE considered at least possibly related to study drug by the Investigator.

Adverse Events of Interest

Bleeding TEAEs (based on SMQ "Haemorrhage") were reported for 49 subjects (69.0%) in the DB caplacizumab group and 49 subjects (67.1%) in the DB placebo group during the Overall Study Period. A total of 22 subjects (78.6%) in the OL caplacizumab group were reported with at least one bleeding-related TEAE.

The most commonly reported bleeding TEAEs were epistaxis (DB caplacizumab group: 23 subjects [32.4%]; DB placebo group: 2 subject [2.7%]) and gingival bleeding (DB caplacizumab group: 13 subjects [18.3%]; DB placebo group: 1 [1.4%]). The majority of bleeding TEAEs in the Overall Study Period were of mild severity (DB caplacizumab group: 27 subjects [38%]; DB placebo group: 27 subjects [37%]).

Most bleeding TEAEs were considered by the Investigator as related to study drug (DB caplacizumab group: 33 subjects [46.5%]; DB placebo group: 17 subjects [23.3%]) during the Overall Study Drug Treatment Period. The majority of bleeding TEAEs considered related to study drug had resolved at the time of the subject's study completion.

Treatment-related bleeding SAEs were reported in 8 subjects (11.3%) in the DB caplacizumab group and 3 subjects (4.1%) in the DB placebo group. The most frequently reported treatment-related bleeding SAE was epistaxis (DB caplacizumab group: 4 subjects [5.6%]; DB placebo group: 0 subjects).

Other Significant Adverse Events

Hypersensitivity reactions (defined by SMQ hypersensitivity) were reported in 24 subjects (33.8%) in the DB caplacizumab group and 22 subjects (30.1%) in the DB placebo group during the Overall Study Period. There were no reports of anaphylaxis to study drug in subjects treated with caplacizumab. Anaphylactic transfusion reaction (i.e., hypersensitivity reactions caused by PE/transfusion) was reported in 1 subject [1.4%] in the DB caplacizumab group and in 3 subjects [4.1%] in the DB placebo group and and allergic transfusion reaction was reported in 2 subjects [2.8%] in the DB caplacizumab group and in 1 subject [1.4%] in the DB placebo group.

The most frequently reported hypersensitivity reactions were urticaria (DB caplacizumab group: 12 subjects [16.9%]; DB placebo group: 5 subjects [6.8%]), rash (DB caplacizumab group: 5 subjects [7.0%]; DB placebo group: 9 subjects [12.3%]), and anaphylactic transfusion reaction (i.e., hypersensitivity reactions caused by PE/ transfusion; DB caplacizumab group: 1 subject [1.4%]; DB placebo group: 3 subjects [4.1%]). All other hypersensitivity reactions occurred in at most 2 subjects per treatment group. No association of hypersensitivity reactions with the presence of pre-Ab and drug-induced TE ADA was found.

The incidence of thromboembolic events, defined per SMQ, was lower in the DB caplacizumab group (14 subjects [19.7%]) compared with the DB placebo group (37 subjects [50.7%]). The most frequently reported thromboembolic events were TTP (DB caplacizumab group: 9 subjects [12.7]; DB placebo group: 29 subjects [39.7%]), deep vein thrombosis (DB caplacizumab group: 3 subjects [4.2%]; DB placebo group: 1 subject [1.4%]), and myocardial infarction (DB caplacizumab group: 1 subject [1.4%]; DB placebo group: 3 subjects [4.1%]). In the OL caplacizumab group, 4 subjects (14.3%) were reported with an event of TTP and 1 subject (3.6%) was reported with an event of vena cava thrombosis.

There were no pregnancies during the study.

Laboratory results

In general, subjects who presented with abnormalities in hematology parameters at Baseline showed an improvement towards a value within normal range at all post-baseline time points that was sustained through the Follow-up Visit (Day 28).

Both treatment groups had elevated mean values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin at Baseline. For all parameters, the values remained stable or returned to within normal range post-baseline in both treatment groups. Abnormally high levels of creatinine and C-reactive protein (CRP) were observed at Baseline and the mean values for both parameters decreased in the course of the study reaching a minimum by Follow-up Visit in both treatment groups. There were no major imbalances between the treatment groups.

The most frequently reported TEAEs related to laboratory abnormalities were hypokalemia (DB caplacizumab group: 6 subjects [8.5%]; DB placebo group: 14 subjects [19.2%]), anemia (DB caplacizumab group: 4 subjects [5.6%]; DB placebo group: 6 subjects [8.2%]), and hyperglycemia (DB caplacizumab group: 4 subjects [5.6%]; DB placebo group: 4 subjects [5.5%]). All laboratory-related TEAEs reported in the DB caplacizumab group were mild or moderate in severity. In the DB placebo group, events of anemia, hyperglycemia, hypokalemia, hypophosphatemia, alanine aminotransferase increased, and gamma glutamyltransferase increased (all reported in 1 subject in the DB placebo group) were reported as severe; all other TEAEs were mild or moderate in severity.

Other Safety Parameters The mean values for vital signs (temperature, pulse, and blood pressure) were similar across the treatment groups. The majority of TEAEs related to vital signs were mild or moderate in severity. There were no major imbalances between the treatment groups with regard to treatment-emergent physical examination abnormalities. All ECG-related TEAEs were mild or moderate in severity, except for an SAE of ventricular fibrillation in 1 subject in the DB caplacizumab group and an SAE of myocardial infarction in 1 subject in the DB placebo group that were reported as severe.
Issue date: 12-Jan-2023