Sponsor: Sanofi **Drug substance:** Caplacizumab	**Study Identifiers:** NCT01151423; EudraCT 2010-019375-30 **Study code:** ALX-0681-2.1/10
Title of the study: A Phase II, single-blind, randomised, placebo-controlled trial to study the efficacy and safety of anti-von Willebrand factor Nanobody administered as adjunctive treatment to patients with acquired thrombotic thrombocytopenic purpura	
Study centers: 32 active sites (out of 56 approved sites) in 11 countries: Australia (1 site), Austria (1 site), Belgium (4 sites), France (1 site), Germany (5 sites), Israel (2 sites), Italy (4 sites), Spain (3 sites), Switzerland (2 sites), United Kingdom (UK; 1 site) and the United States of America (USA; 8 sites).	
Study period: Date first participant enrolled: 07/Jan/2011 Date last participant completed: 14/Mar/2014 Study Status: Completed	
Phase of development: Phase II study	
Objectives: Primary ● Reduction of time-to-response, defined by the achievement of platelet count response, confirmed at 48 hours after the initial reporting of this response. Secondary (including longer-term disease sequelae) ● Improvement in number of subjects responding to therapy ● Reduction in plasma exchange (PE) procedure-related items ● Reduction of time to resolution or improvement of symptoms typical of thrombotic thrombocytopenic purpura (TTP), including blood markers ● Reduction of number of exacerbations (defined as recurrent thrombocytopenia following a response and requiring a re-initiation of daily PE treatment after ≥ 1 day but ≤ 30 days after the last daily PE) and relapses (defined as de novo event of TTP that occurs later than 30 days after the last daily PE) ● Improvement of cognitive level at steady state post-acute phase (adults only) ● Improvement of clinical symptoms and organ function ● Reduction in mortality within the PE treatment period and within the subsequent study drug treatment period (including tapering) ● Reduction of concomitant treatment-related complications ● Evaluation of safety and immunogenicity of adjunctive treatment with ALX-0081 ● Determination of pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of ALX-0081 in subjects with acquired TTP.	

Methodology:

This was a Phase II multicentre, single-blind, parallel design, randomised, placebocontrolled study. The main study population was adult symptomatic subjects with acute episodes of acquired TTP, requiring treatment with PE. After confirmation of eligibility for study participation, adult subjects were randomised in a ratio of 1:1 to either receive ALX-0081 or placebo.

Subjects received a first intravenous (i.v.) bolus of 10 mg ALX-0081 or placebo via push injection within 6 hours to 15 minutes prior to the initiation of PE on-study. The first PE on-study could either be the very first PE session for the current episode of acquired TTP (if the subject was randomised prior to the initiation of PE, majority of subjects) or the second PE session (if the subject was randomised after a single PE session). The first PE on-study was followed by subcutaneous (s.c.) administration of 10 mg study drug within 30 minutes after the end of the PE procedure.

Subsequently, daily s.c. administrations of 10 mg ALX-0081 or placebo were given within 30 minutes after the end of the PE procedure for the duration of PE (including tapering and PE given for exacerbations) and once daily for 30 days following the last PE. The total daily dose of study drug was 10 mg when administered in conjunction with PE and 10 mg when in the period following the last PE. If 2 PE sessions were scheduled per day, study drug was administered within 30 minutes after the end of the PE procedure resulting in a daily dose of 20 mg. If less than daily PE was scheduled (i.e., during a tapering regimen), study drug was administered daily. Study drug administration continued in case of re initiation of PE for an exacerbation of TTP with a maximum total treatment duration limited to 90 days after first administration of study drug.

To meet the requirements outlined in the EU PIP, in centres where the IEC/IRB and the Investigator agreed, the study was open for the recruitment of adolescent subjects (12 to < 18 years) who met the eligibility criteria. Adolescent subjects were not to be randomised, and were to receive only ALX-0081. Adolescent subjects were to receive weight-based doses according to the same administration schedule as adults.

Up to 30 days after the last day of study drug administration, subjects were assessed for the primary and secondary endpoints of the study and were to be followed for a maximum of 1 year for relapses and other tertiary (longer-term) endpoints. Laboratory parameters for inclusion, study conduct, safety assessments and assessments of response/relapse, re-treatment and study drug dose modification were assessed at each local site laboratory. PD and PK parameters were analysed at a central or specialty laboratory.

An independent Data Safety Monitoring Board (DSMB) monitored accruing safety data during the study and made recommendations regarding the continuation of the study.

Number of participants:

Planned: 110 adult subjects; Randomised: 75 adult subjects (36 to ALX-0081 and 39 to placebo)

In addition, the study was open for the recruitment of adolescent subjects. No adolescent subjects were recruited.

The study was stopped early due to the low recruitment rate when the last randomised subject reached the 1-month follow-up visit. For all subjects who did not complete the 12-month follow-up visit, an unscheduled visit was performed if the subject did not have a per-protocol visit prior to study closure.

Diagnosis and criteria for inclusion:

The target population for this study included symptomatic subjects with acute episodes of acquired TTP, requiring treatment with PE. The main criteria for inclusion were:

1. 18 years of age or older (adults) or aged 12 to < 18 years (adolescents).

2. Male or female, willing to accept an acceptable contraceptive regimen.

3. Patients with clinical diagnosis of TTP.

4. Necessitating PE (one single PE session prior to randomisation into the study is allowed).

5. Subject accessible to follow-up.

6. Obtained signed and dated informed consent and assent (if applicable, for adolescents).

Test product:

ALX-0081 was administered at specific times relative to the PE procedures. In adults, each study drug administration consisted of 10 mg of ALX-0081. The first study drug administration was a single i.v. bolus, administered by a push injection, followed by s.c. administration. All subsequent study drug administrations were daily s.c. injections within 30 minutes after the end of the PE procedure if applicable or within 24 hours of the previous dose.

Adolescent subjects were to receive weight-based doses according to the same administration schedule as adults.

Duration of treatment:

The Treatment Phase was of variable duration due to the platelet recovery dependent duration of PE treatment, up to a maximum of 90 days. It comprised a daily s.c. treatment phase of variable duration: in conjunction with daily PE, Day 1 after the last daily PE, in conjunction with PE tapering if applicable, and 30 days of study drug post-PE.

This report presents the results obtained from the study, which includes data up to 1 month follow-up for all subjects, as well as the results at the available time points between 1 month and 12 months follow-up for all of the subjects who continued in the study beyond the 1-month follow-up visit, including those who did not reach 12 months follow-up due to early termination of the study.

Criteria for evaluation:

Primary endpoint:

Time-to-response based on the following criteria:

- Recovery of platelets ≥ 150,000/µL.

This response had to be confirmed at 48 hours after the initial reporting of platelet recovery ≥ 150,000/ μ L by a de novo measure of platelets ≥ 150,000/ μ L and lactate dehydrogenase (LDH) ≤ 2 x upper limit of normal (ULN) (i.e., "confirmed platelet response").

Secondary endpoints:

All endpoints achieved from randomisation within a 30 day (inclusive) period after the end of study drug treatment:

- Number and percentage of subjects with complete remission (defined as confirmed platelet response and absence of exacerbation)
- Number and percentage of (subjects with) exacerbations of TTP (defined as recurrent thrombocytopenia following a confirmed platelet response and requiring a re-initiation of daily PE treatment after ≥ 1 day but ≤ 30 days after the last daily PE) and time to first exacerbation of TTP
- Number and percentage of subjects relapsing of TTP (defined as de novo event of TTP that occurs later than 30 days after the last daily PE)
- Number of daily PE sessions, total volume of plasma administered and number of days of daily PE
- Total mortality within the PE treatment period and within the subsequent study drug treatment period (including tapering)
- Number and percentage of subjects with platelets ≥ 150,000/µL at Day 30 of study drug administration (last treatment day visit) and 1 month follow-up time point

- Resolution or improvement (improvement of ≥ 1 grade in the Common Terminology Criteria for Adverse Events [CTCAE] v4.0 scale) of TTP-related signs and symptoms as captured on physical examination and as adverse event (AE), at complete remission and at end of the study drug treatment period (including tapering) (by number of unique subjects and by total number of AEs)
- Incidence of PE treatment-related AEs, such as, but not restricted to: haemorrhage from catheter insertion, sepsis, catheter thrombosis, pneumothorax, fluid overload, hypoxia, hypotension, anaphylactoid reactions and transfusion-related acute lung injury (TRALI)
- Incidence and severity of ALX-0081 treatment emergent adverse events (TEAEs) and relationship to study drug.
- Development of anti-drug antibodies (ADA) ≤ 30 days post-last study drug treatment
- PK and PD profile.

Post-hoc analysis:

- Volume of PE and number of PE days summarised by actual treatment and by study period (daily PE period, post-Daily PE period on treatment, and post-Treatment period until 1 month follow-up after daily PE), based on the safety population.
- ADAMST13 activity as marker for underlying disease activity in relation to recurrent TTP disease.
- Exploratory Kaplan-Meier analysis of time to normalisation of troponin (TnT or TnI), creatinine and LDH values.
- Bleeding- and immune-related TEAEs

Statistical methods:

All data were summarised by treatment group. In addition, where appropriate, a total column was included to summarise all subjects.

All hypothesis testing was 2-sided unless otherwise specified and carried out at the 5% significance level.

The primary, secondary and longer term endpoint analyses were based on available data. No imputations were made for missing data unless otherwise specified.

The primary efficacy endpoint, time-to-response, was measured in days, hours and minutes from date of first study drug administration. A Kaplan-Meier (KM) analysis with time-to-response as the endpoint and treatment group as the independent variable and stratified for absence/presence of one PE session prior to randomisation was performed on the Intent-to-Treat (ITT). An observation was censored if it did not meet the defined time interval of 30 days after first administration of study drug, due to any cause of loss-to follow-up (including death), or endpoint not being reached.

ALX-0081 was compared with placebo using a one-sided log-rank test in order to assess superiority at 2.5% significance level. The log-rank test was one-sided because a reduction in time-to-response by ALX-0081 was expected compared with placebo due to an inhibition of von Willebrand Factor (vWF) by ALX-0081 (based on pre-clinical data).

In addition to the KM estimates, the corresponding Cox proportional hazard regression model with Baseline disease characteristics (A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 [ADAMTS13] activity < 5% versus ≥ 5%, vWF level [continuous], first episode versus recurrent disease, presence or absence of ristocetin cofactor [RICO] suppression of < 20% throughout treatment period, one PE prior to randomisation or not) was used to estimate the hazard ratio (HR) and associated 95% confidence intervals (CIs) for the HR for ALX-0081 and the placebo group. Results of these analyses are discussed in the body of the Clinical Study Report.

Sensitivity analyses comprised of analyses performed on the PP Population for the primary efficacy endpoint; analysis of the treatment effect adjusted for various covariates, such as ADAMTS13 activity at Baseline; analysis of non-confirmed and confirmed platelet response; and assessment of impact (potential bias) of the use of rituximab during daily PE. Results of these analyses are discussed in the body of the Clinical Study Report.

All safety parameters were summarised descriptively by treatment group. Continuous laboratory variables were summarised as actual result, change from Baseline and percentage change from Baseline for all available visits by treatment group. Shift tables were presented for haematology, coagulation and chemistry parameters. Subject profile plots of PD parameters and summary statistics by PD parameter and treatment were presented for the Safety Population.

An independent DSMB monitored accruing safety data during the study (SAEs on an ongoing basis and an ‘early safety look’, per protocol, when 16 subjects, 8 ALX-0081-treated and 8 placebo-treated, had completed treatment with study drug). Based on the ‘early safety look’, the DSMB recommended to the Sponsor that the study could continue with no changes to the Protocol.

An interim analysis for safety with formal stopping rules was performed when 28 of the ALX-0081 treated subjects had been treated and assessed. Upon review of the interim safety analysis, the DSMB made the recommendation to continue the study with no changes to the protocol. The procedures and responsibilities for the collection, analysis, and review of the data by the DSMB as well as communication and documentation of their opinions and recommendations were defined in the DSMB charter.

Summary Results:

Efficacy:

The primary endpoint, time to confirmed platelet response, was significantly faster in the ALX-0081 treatment group, compared with the placebo group (p=0.005), taking into account presence or absence of one PE session prior to randomisation as demonstrated by a hazard ratio (95% CI) for the ALX-0081 versus placebo treatment group of 2.197 (1.278, 3.778). In the subjects who did not receive a PE session within 24 hours prior to randomisation (n = 69), the median time to response was 3.00 (2.74, 3.88) days in the ALX-0081 treatment group and 4.92 (3.21, 6.59) days in the placebo treatment group. In the subjects who received a PE session within 24 hours prior to randomisation (n = 6), the median time to response (95% CI) was 2.44 (1.92, 2.97) days in the ALX-0081 treatment group compared with 4.31 (2.91, 5.68) days in the placebo treatment group.

Complete remission following initial daily PE was observed in a higher number and proportion of subjects in the ALX-0081 treatment group compared with the placebo treatment group (29 [80.6%] subjects in the ALX-0081 treatment group [95% CI: 64.0, 91.8] versus 18 [46.2%] subjects in the placebo treatment group [95% CI: 30.1, 62.8]).

Exacerbations of TTP within 30 days of the last day of initial daily PE occurred in fewer subjects in the ALX-0081 treatment group (3 [8.3%] subjects; 95% CI: 1.8, 22.5) compared with the placebo treatment group (11 [28.2%] subjects; 95% CI: 15.0, 44.9).

Relapse of TTP (event of TTP that occurred later than 30 days after the last daily PE) occurred in more subjects in the ALX-0081 treatment group (11 [30.6%] subjects; 95% CI: 16.3, 48.1) compared with the placebo treatment group (3 [7.7%] subjects; 95% CI: 1.6, 20.9). In eight subjects in the ALX-0081 treatment group the relapse occurred within 30 days of the interruption per protocol of ALX-0081. Seven of these 8 subjects relapsed within 4-10 days after stopping ALX- 0081 and had continuous ADAMTS13 activity <10% during the treatment period indicative of unresolved underlying auto-immune activity (post-hoc analysis).

The mean (±SD) number of PE days during the daily PE period on treatment was 5.9 (±2.43) in the ALX-0081 treatment group and 7.9 (±6.43) in the placebo group. During the post-daily PE treatment period, the mean (±SD) number of PE days was 4.5 (±3.84) and 7.0 (±5.28), respectively.

Over the whole study period (until 1 month follow-up), the mean number of PE days was 10.2 (±6.64) and 11.7 (8.45), respectively.The mean (±SD) volume during the daily PE period on treatment was 19923 (±8177.7) in the ALX-0081 treatment arm and 28307 (±21393.7) mL in the placebo group. During the post-daily PE treatment period, the mean (±SD) volume was 14305 (±12157.6) and 25025 (±23478.4) mL, respectively. Over the whole study period (until 1 month follow-up), the mean was 36014 (±25935.3) and 41834 (31183.2) mL, respectively. (Post-hoc analysis).

No deaths occurred within the daily PE period or within the study treatment period. There were 2 deaths between the end of study treatment up to and including 1 month follow-up, both in the placebo treatment group (5.1% of subjects in the placebo treatment group).

Platelet counts were ≥ 150,000/ μ L in more subjects in the ALX-0081 treatment group (33 [91.7%]; 95% CI: 77.5, 98.2) compared with the placebo treatment group (30 [76.9%]; 95% CI: 60.7, 88.9) at Day 30 of study drug administration (the date of last administration of study drug). At 1 month follow-up platelet counts were ≥ 150,000/ μ L in 29 (80.6%) subjects in the ALX-0081 treatment group (95% CI: 64.0, 91.8) compared with 30 (76.9%) subjects in the placebo treatment group (95% CI: 60.7, 88.9).

PD assessments: Mean RICO activity was mostly suppressed to < 20% throughout the treatment period, vWF:Ag levels, and FVIII:C levels in the ALX 0081 treatment group generally decreased during the treatment phase, and were lower than placebo throughout the treatment period. After ALX 0081 treatment was stopped, mean RICO activity recovered and vWF:Ag levels, and FVIII:C levels increased and were similar to levels in the placebo treatment group by 1 month follow up, if not earlier.

PK data showed that in the ALX-0081 treatment group, the mean ALX-0081 concentration increased rapidly to a peak at 5 to 10 minutes after the first ALX-0081 administration (as an i.v. bolus). Mean ALX-0081 plasma concentrations reached a steady state during the treatment period with s.c. administration of ALX-0081. After ALX-0081 treatment was stopped, mean ALX-0081 plasma concentrations decreased and were below limit of quantification by 1 month follow-up.

Exploratory analysis (post-hoc analysis) showed a trend towards more rapid normalisation of organ damage markers, for LDH, troponin and creatinine.

Safety results:

The overall duration of exposure to study drug was similar between the two treatment groups. A total of 574 TEAEs were reported in 34 (97.1%) subjects in the ALX-0081 treatment group compared with 545 TEAEs in 37 (100%) subjects in the placebo treatment group. The most common TEAEs by System Organ Class (SOC) occurring in the study were 'gastrointestinal disorders' and 'nervous system disorders' in both treatment groups.

Most TEAEs, overall and by treatment group were of mild severity. Severe TEAEs occurred in a higher proportion of subjects in the ALX-0081 treatment group compared with the placebo treatment group (18 [51.4%] versus 14 [37.8%] subjects, respectively).

Two subjects in the placebo treatment group died between the end of study treatment (one of which was discontinuation due to the AE leading to death), up to and including 1 month follow up. Both deaths were considered to be unlikely/not related to the study drug. No subjects in the ALX-0081 treatment group died during the study.

Serious TEAEs were reported in 20 (57.1%) subjects in the ALX-0081 treatment group and 19 (51.4%) subjects in the placebo treatment group. The most commonly reported serious TEAEs by SOC were 'blood and lymphatic system disorders', which were reported in a similar proportion of subjects in the ALX-0081 (14 [40.0%] subjects) and placebo (13 [35.1%] subjects]) treatment groups, followed by 'nervous system disorders', which were reported in a higher proportion of subjects in the ALX-0081 treatment group (5 [14.3%] subjects) than in the placebo treatment group (3 [8.1%] subjects]). Serious treatment-emergent drug related AEs were reported in 7 (20%) subjects in the ALX-0081 group and no subjects in the placebo treatment group.

The incidence of clinically relevant bleeding was low in both treatment groups, but was higher in the ALX-0081 treatment group compared with the placebo treatment group during the first week of daily PE (6 subjects versus 2 subjects). No subjects in either treatment group had clinically relevant bleeding on Days 3 or 7 of follow-up or at 1, 2, 3, 6, or 12 months follow-up. Low levels of bleeding, as demonstrated by low mean modified ITP bleeding scores, were observed at Baseline and throughout the study in both treatment groups.

The number and proportion of subjects with any bleeding-related TEAE was higher in the ALX-0081 treatment group (19 [54.3] subjects) than in the placebo treatment group (14 [37.8%] subjects); most bleeding-related TEAEs were mild (84/101 events [83.2%]) or moderate (14/101 events [13.9%) in severity. Amongst the bleeding-related TEAE epistaxis was the most common Preferred Term (16 events in 11 subjects [31.4%] for ALX-0081 and 8 events in 4 subjects [10.8%] for placebo (all mild or moderate). Two subjects in each treatment arm experienced serious bleeding related TEAEs, with a fatal outcome for one of the subjects receiving placebo. Anaemia was reported in a lower proportion of subjects in the ALX-0081 treatment group (3 [8.6%] subjects) compared with the placebo treatment group (8 [21.6%] subjects). Only 2 cases of anaemia (2 subjects [5.7%] in the ALX-0081 group) were considered severe; one of these 2 cases was considered serious. (Post-hoc analysis).

The number and proportion of subjects with any immune-related TEAE was higher in the ALX-0081 treatment group (17 [48.6%] subjects) than in the placebo treatment group (12 [32.4%] subjects); most immune-related TEAEs were mild (43/65 events [66.2%]) or moderate (20/65 events [30.8%) in severity. Only one subject in the ALX-0081 group experienced a serious TEAE of allergic dermatitis during the PE period, which was considered moderate in intensity and possibly related to the study drug and related to PE. This subject also experienced 2 non-serious TEAEs of vaccination site reaction during the PE period which were both considered severe in intensity and unlikely/not related to the study drug. (Post-hoc analysis).

The number and proportion of subjects with any TEAE leading to discontinuation of study drug was low in both treatment groups, but was higher in the ALX-0081 treatment group (4 [11.4%] subjects) than in the placebo treatment group (2 [5.4%] subjects).

There were no clinically relevant differences between the treatment groups for haematology parameters (excluding platelets, efficacy parameter) or for blood chemistry.

No remarkable findings or differences between the treatment groups were observed regarding physical examination and vital signs results.

Pre-existing antibodies were detected pre-dose in 13% of the subjects. Treatment-emergent antidrug antibodies (TE ADA) were detected in 9% of the subjects in the ALX-0081 treated group and no TE ADA was detected in the placebo treated subjects. Immunogenicity in the ALX-0081 treated group (pre-Ab and/or TE ADA) had no apparent influence on PK/PD parameters.

Also no association was found between pre-Ab or TE ADA and safety findings.

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