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BRIEF REPORT

Caplacizumab reduces the frequency of major thromboembolic events, exacerbations and death in patients with acquired thrombotic thrombocytopenic purpura

F. PEYVANDI,* M. SCULLY,† J. A. KREMER HOVINGA,‡ P. KNÖBL,§ S. CATALAND,¶ K. DE BEUF,** F. CALLEWAERT,** H. DE WINTER** and R. K. ZELDIN**

**Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Ca' Granda Ospedale Maggiore Policlinico, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; †Department of Haematology, University College London Hospital, London, UK; ‡University Clinic of Hematology & Central Hematology Laboratory, Inselspital, Bern University Hospital and Department of Clinical Research, University of Bern, Bern, Switzerland; §Department of Medicine 1, Division of Hematology and Hemostasis, Medical University of Vienna, Vienna, Austria; ¶Department of Internal Medicine, Ohio State University, Columbus, OH, USA; and **Ablynx NV, Zwijnaarde, Belgium*

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Essentials

- Acquired thrombotic thrombocytopenic purpura (aTTP) is linked with significant morbidity/mortality.
- Caplacizumab's effect on major thromboembolic (TE) events, exacerbations and death was studied.
- Fewer caplacizumab-treated patients had a major TE event, an exacerbation, or died versus placebo.
- Caplacizumab has the potential to reduce the acute morbidity and mortality associated with aTTP.

Summary. *Background:* Acquired thrombotic thrombocytopenic purpura (aTTP) is a life-threatening autoimmune thrombotic microangiopathy. In spite of treatment with plasma exchange and immunosuppression, patients remain at risk for thrombotic complications, exacerbations, and death. In the phase II TITAN study, treatment with caplacizumab, an anti-von Willebrand factor Nanobody® was shown to reduce the time to confirmed platelet count normalization and exacerbations during treatment. *Objective:* The clinical benefit of caplacizumab was further investigated in a *post hoc* analysis of the incidence of major thromboembolic events and exacerbations during the study drug treatment period and thrombotic thrombocytopenic purpura-related death during the study. *Methods:* The Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) for 'embolic and thrombotic events' was run to investigate the occurrence of major thromboembolic events and exacerbations in the safety population of the TITAN study, which consisted of 72 patients, of whom 35 received caplacizumab and 37 received placebo. *Results:* Four events (one pulmonary embolism and three aTTP exacerbations) were reported in four patients in the caplacizumab group, and 20 such events were reported in 14 patients in the placebo group (two acute myocardial infarctions, one ischemic stroke, one hemorrhagic stroke, one pulmonary embolism, one deep vein thrombosis, one venous thrombosis, and 13 aTTP exacerbations). Two of the placebo-treated patients died from aTTP during the study. *Conclusion:* In total, 11.4% of caplacizumab-treated patients and 43.2% of placebo-treated patients experienced one or more major thromboembolic events, experienced an exacerbation, or died. This analysis shows the potential for caplacizumab to reduce the risk of major thromboembolic morbidities and mortality associated with aTTP.

Keywords: caplacizumab; morbidity; mortality; purpura, thrombotic thrombocytopenic; von Willebrand factor.

Correspondence: Robert K. Zeldin, Clinical Development, Ablynx NV, Technologiepark 21, 9052 Zwijnaarde, Belgium.
Tel.: +32 9262 0000.
E-mail: robert.zeldin@ablynx.com

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Introduction

Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare, life-threatening autoimmune blood clotting disorder, manifested by systemic microvascular thrombosis leading to profound thrombocytopenia, hemolytic anemia, and organ ischemia [1]. It is caused by inhibitory autoantibodies against the von Willebrand factor

(VWF)-cleaving protease ADAMTS-13 [2]. Decreased ADAMTS-13 activity leads to an accumulation of ultra large (UL) VWF multimers, which bind to platelets and induce the formation of microthrombi, causing tissue ischemia and organ dysfunction, and possibly resulting in overt major thromboembolic complications, such as stroke, myocardial infarction, and arterial and venous thrombosis [3,4]. Episodes of aTTP are associated with an acute mortality rate of up to 20% [5], with most deaths occurring within 30 days of diagnosis [6] (median of 9 days [3]).

The current mainstay of aTTP treatment is plasma exchange (PE) in conjunction with immunosuppression (e.g. with glucocorticoids and/or rituximab) [7]. PE removes UL VWF and autoantibodies and replenishes ADAMTS-13, whereas immunosuppression inhibits autoantibody formation. However, current treatment has a slow onset of action and does not immediately address the pathophysiologic platelet aggregation that leads to the formation of microthrombi [8].

Caplacizumab, an anti-VWF Nanobody®, immediately blocks the interaction of UL VWF with platelets, and therefore inhibits further formation and accumulation of microthrombi. The efficacy and safety of caplacizumab have been evaluated in the phase II TITAN study [9]. Seventy-five patients with a clinical diagnosis of aTTP were randomized. Although ADAMTS-13 activity was not included in the eligibility criteria, 77% of patients had a baseline ADAMTS-13 activity of $< 10\%$, and 11% had ADAMTS-13 activity levels of $\geq 10\%$; baseline ADAMTS-13 results were missing for the remaining 12%. The results of the study showed that treatment with caplacizumab resulted in 39% faster normalization of platelet counts than treatment with placebo [9]. This translated into a reduced need for PE treatment (7.7 days versus 11.7 days for placebo). Treatment with caplacizumab was also associated with a higher complete remission rate (i.e. confirmed platelet count response and absence of exacerbation) (81% versus 46% for placebo), fewer exacerbations during the treatment period (three patients versus 11 for placebo), and a reduction in the percentage of patients refractory to treatment (5.7% versus 21.6%, or 0% versus 10.8% for placebo, depending on the definition used for refractoriness [10]). Seven patients in the caplacizumab group experienced a relapse within 10 days after stopping use of the study drug. All had ADAMTS-13 levels that remained below 10%, suggesting unresolved autoimmune activity. The main safety finding was increased mild bleeding, mainly mucocutaneous, without a requirement for VWF/factor VIII administration.

Here, we report the results of a *post hoc* analysis of the TITAN study data that evaluated the impact of treatment with caplacizumab on the incidence of major thromboembolic events and exacerbations during the study drug treatment and aTTP-related mortality during the study.

Methods

The phase II TITAN study was a randomized, single-blind, placebo-controlled, multicenter study in adults experiencing an acute episode of aTTP [9]. The main inclusion criteria were a clinical diagnosis of aTTP requiring the initiation of PE, and a platelet count of $< 100\,000\ mm^{-3}$.

Seventy-five patients were randomized in a 1 : 1 ratio to receive either 10 mg of caplacizumab or placebo daily in addition to standard of care throughout the PE period and for 30 days thereafter. The safety population (i.e. all patients who received at least one dose of study drug) consisted of 72 patients, of whom 35 received caplacizumab and 37 received placebo, and was used for this analysis.

Major thromboembolic events were retrieved from the study's safety database (i.e. all adverse events as reported by the Investigators) by use of the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) for 'embolic and thrombotic events'. This query contains predetermined sets of MedDRA preferred terms for 'arterial', 'venous' and 'vessel type unspecified and mixed arterial and venous' events (MedDRA version 19.1 was used). Medical review of the output resulted in exclusion of two reported treatment-emergent adverse events from the analysis. One event was reported as 'thrombotic catheter', but was an obstruction within the malfunctioning catheter itself and not a venous thrombosis. The second event was reported as 'thrombocytopenia', but was present at baseline. Transient ischemic attacks were not considered to be major thromboembolic events, and were therefore also not included in this analysis. 'Thrombotic thrombocytopenic purpura' is a predefined term in the SMQ 'thrombotic and embolic events'. aTTP exacerbations are captured in the SMQ output, as they reflect acute worsening of the presenting episode. They are reported as 'aTTP exacerbations'. Thrombotic thrombocytopenic purpura (TTP)-related mortality during the study was evaluated on the basis of adverse event reporting, with relatedness to aTTP as judged and reported by the investigator. The number of events and the number and percentage of patients having an event or who died were summarized by treatment group for the safety population. The event times of major thromboembolic events, TTP exacerbations and TTP-related death were presented graphically by treatment group.

Results and discussion

After medical review of the events defined by the SMQ, a total of eight major thromboembolic events were identified (Table 1). One major thromboembolic event was reported in one patient in the caplacizumab group: pulmonary embolism. In the placebo group, seven major thromboembolic events were reported in six patients: two

Table 1 Treatment-emergent major thromboembolic events and acquired thrombotic thrombocytopenic purpura (aTTP) exacerbations during the treatment period and overall aTTP-related mortality in the safety population of the phase II TITAN study

	Caplacizumab (N = 35)			Placebo (N = 37)		
	No. of events	No. of patients	% of patients	No. of events	No. of patients	% of patients
Major thromboembolic events (based on the SMQ, by preferred term)						
Acute myocardial infarction*	0	0	0	2	2	5.4
Pulmonary embolism	1	1	2.9	1	1	2.7
Deep vein thrombosis†	0	0	0	1	1	2.7
Venous thrombosis‡	0	0	0	1	1	2.7
Ischemic stroke§	0	0	0	1	1	2.7
Hemorrhagic stroke§	0	0	0	1	1	2.7
aTTP exacerbations (based on the SMQ, by preferred term)						
Thrombotic thrombocytopenic purpura¶	3	3	8.6	13	11	29.7
aTTP-related mortality						
Deaths related to TTP	0	0	0	2	2	5.4
Total	4	4**	11.4	22	16**	43.2

SMQ, Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query; TTP, thrombotic thrombocytopenic purpura. *Verbatim terms: one acute myocardial infarction was reported as 'non S-T elevation myocardial infarction', and one as 'acute myocardial infarction'. †Verbatim term: 'right lower extremities deep vein thrombosis'. ‡Verbatim term: 'gemellar muscular veins thrombosis'. §The ischemic stroke and hemorrhagic stroke were reported as separate events within the same patient. Both events had the same onset and end date. ¶This preferred term consisted of recurrences of aTTP during the treatment period, defined and reported per protocol as exacerbations of TTP. **A patient may have experienced more than one event.

acute myocardial infarctions in two patients (reported verbatim terms were 'non S-T elevation myocardial infarction' and 'acute myocardial infarction', respectively), one ischemic stroke and one hemorrhagic stroke in one patient (reported as separate events within the same patient; both events had the same onset and end date), one pulmonary embolism, one deep vein thrombosis (the reported verbatim term was 'right lower extremities deep vein thrombosis'), and one venous thrombosis (the reported verbatim term was 'gemellar muscular veins thrombosis'). The frequency of major thromboembolic events in the placebo group was consistent with that reported in the literature [3,4].

The output of the SMQ also reflects the aTTP exacerbations that were reported as serious adverse events during the study drug treatment period. In total, three aTTP exacerbations occurred in three caplacizumab-treated patients, and 13 aTTP exacerbations occurred in 11 placebo-treated patients (Table 1). TTP exacerbations re-expose patients to the same acute thrombotic risks of the disease. In the French TTP Registry, death was reported in 14% of the patients with an exacerbation [11].

Two patients died during the study, both in the placebo group (Table 1). One patient died from severe refractory TTP, after 22 days of intensified daily PE treatment and immunosuppressive treatment (i.e. cyclophosphamide and rituximab). The second patient died from a cerebral hemorrhage after 10 days of daily PE, throughout which platelet counts were in the range of 30×10^9 L^{-1}. These findings are consistent with published data showing that refractoriness to treatment is an indicator of a poor prognosis for survival in patients with aTTP [12–14]. It is of note that caplacizumab has been shown to reduce the incidence of refractoriness to therapy [10].

The composite analysis of major thromboembolic events and aTTP exacerbations during the study drug treatment period and aTTP-related deaths during the study showed that 11.4% of caplacizumab-treated patients and 43.2% of placebo-treated patients experienced one or more thromboembolic events, experienced an exacerbation, or died, which represents a 74% reduction (Table 1). All reported events occurred in patients with a baseline ADAMTS-13 activity of < 10%, except for three events in three placebo-treated patients: one patient with a myocardial infarction (missing baseline ADAMTS-13 result), one patient with a fatal cerebral hemorrhage (baseline ADAMTS-13 activity of 75%), and one patient with an exacerbation (baseline ADAMTS-13 activity of 90%). It is of note that, if these patients had been excluded from the analysis, the results would have still favored caplacizumab.

The time-to-event analysis indicates that the majority of these events occurred within the first 30 days of enrollment (Fig. 1). Most of the major thromboembolic events occurred during the daily PE period, whereas, by definition, aTTP exacerbations occurred after an initial platelet response had been reached (range: within 7–30 days of enrollment). These data confirm that patients experiencing an aTTP episode are at the greatest risk of life-threatening complications during this acute period.

Major thromboembolic events may contribute to long-term cognitive and physical deficits of patients

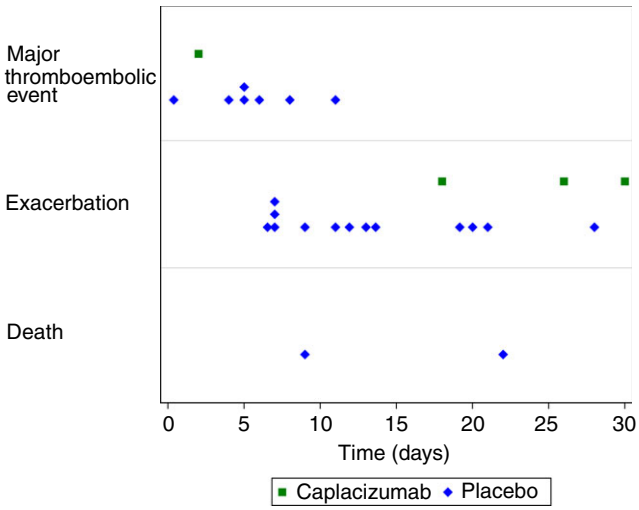

Fig. 1. Event times of major thromboembolic events, thrombotic thrombocytopenic purpura (TTP) exacerbations and TTP-related death by treatment group. Time is expressed as days from the first dose of the study drug.

experiencing an episode of aTTP [15–20]. The impact of treatment with caplacizumab on the frequency of major thromboembolic events and exacerbations in the phase II TITAN study was highly clinically meaningful. By reducing acute thromboembolic complications and exacerbations, treatment with caplacizumab may also improve longer-term outcomes. A phase III study of caplacizumab in patients with aTTP is ongoing (NCT02553317), and will prospectively evaluate these important clinical endpoints as a composite endpoint consisting of major thromboembolic events, exacerbations, and aTTP-related death. In addition, patients who completed the phase III study will be followed in a long-term follow-up study (NCT02878603).

Addendum

F. Peyvandi designed research, performed research, collected data, analyzed and interpreted data, and reviewed the manuscript. M. Scully designed research, performed research, collected data, analyzed and interpreted data, and reviewed the manuscript. J. A. Kremer Hovinga designed research, performed research, collected data, analyzed and interpreted data, and reviewed the manuscript. P. Knöbl designed research, performed research, collected data, analyzed and interpreted data, and reviewed the manuscript. S. Cataland designed research, analyzed and interpreted data, and reviewed the manuscript. K. De Beuf designed research, analyzed and interpreted data, and performed analysis. F. Callewaert designed research, analyzed and interpreted data, and wrote the manuscript. H. De Winter designed research, analyzed and interpreted data, and wrote the manuscript. R. K. Zeldin designed research, analyzed and interpreted data, and wrote the manuscript.

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Disclosure of Conflict of Interests

P. Knöbl reports personal fees from Ablynx during the conduct of the study; and grants and personal fees from Shire, Novo Nordisk, Alexion, and CSL Behring outside the submitted work. F. Callewaert has a patent on "Stable formulations of immunoglobulin single variable domains and uses thereof" (PCT/EP2014/060107; NL 1040254) pending. F. Peyvandi reports grants and personal fees from Ablynx during the conduct of the study; and personal fees from Bayer, Grifols, Novo Nordisk, Sobi, Alexion, Kedrion Biopharma, Freeline, LFB, Octapharma, and F. Hoffmann-La Roche Ltd outside the submitted work.J. H. Kremer reports personal fees from Ablynx during the conduct of the study; an unrestricted grant from Baxalta outside the submitted work. M. Scully reports personal fees from Ablynx during the conduct of the study and involvement in the Phase II study; fees from Ablynx, Novartis, and Alexion, as well as grants from Baxalta outside the submitted work. S. Cataland reports personal fees from Ablynx outside the submitted work. The other authors state that they have no conflict of interest.

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