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Efficacy and safety of open-label caplacizumab in patients with exacerbations of acquired thrombotic thrombocytopenic purpura in the HERCULES study

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Running header (50/50 characters max.): Caplacizumab in patients with exacerbation of aTTP

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Essentials

- In the double-blind (DB) part of HERCULES, caplacizumab was shown to be safe and effective
- Following exacerbation during DB treatment, patients were treated with open-label caplacizumab
- Caplacizumab was efficacious in patients with an exacerbation (mainly from the DB placebo group)
- The safety profile was consistent with the DB period (increased mucocutaneous bleeding)

Summary

Background: Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare, life-threatening autoimmune thrombotic microangiopathy. Caplacizumab, an anti-von Willebrand Factor Nanobody®, is effective for treating aTTP episodes and is well tolerated.

Objectives and Methods: In the phase 3 HERCULES trial (NCT02553317), patients with aTTP received double-blind caplacizumab or placebo during daily therapeutic plasma exchange (TPE) and for ≥30 days thereafter. Patients who experienced an exacerbation while on blinded study drug treatment switched to receive open-label caplacizumab plus re-initiation of daily TPE. Exacerbations were defined as recurrence of disease occurring within 30 days after cessation of daily TPE.

Results: Thirty-one patients (placebo, n = 28; caplacizumab, n = 3) had an exacerbation during double-blind treatment. Twenty-eight patients switched to open-label caplacizumab (placebo, n = 26; caplacizumab, n = 2); the three others discontinued upon exacerbation. Median time to platelet count response (≥150 x 10^9/L) was 3.49 days upon receiving caplacizumab. There were no deaths. During open-label treatment, further exacerbation or a major thromboembolic event (vena cava thrombosis) was experienced by one patient (3.6%) each. Consistent with the double-blind phase, the most frequent treatment-emergent adverse events were catheter site hemorrhage (28.6%), headache (21.4%), and epistaxis (17.9%).

Conclusions: These results suggest that caplacizumab was efficacious and well tolerated in patients with aTTP who experienced a disease exacerbation during double-blind treatment in HERCULES.

Key words: Caplacizumab; von Willebrand Factor; Plasma Exchange; Purpura, Thrombotic Thrombocytopenic; ADAMTS13 Protein

1 | INTRODUCTION

Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare thrombotic microangiopathy, characterized by severe thrombocytopenia, microangiopathic hemolytic anemia, and organ ischemia, caused by a deficiency in ADAMTS13 activity [1,2]. The lack of ADAMTS13 activity means ultra-large multimers of von Willebrand factor (vWF) are no longer adequately processed and cleaved. This allows unrestrained vWF-mediated platelet adhesion in the microvasculature [3,4], which, if left untreated, is fatal in >90% of cases [3,5]. Although daily therapeutic plasma exchange (TPE) and immunosuppression has improved patient outcomes, acute mortality is still ~10 to 20% [6-12], and patients are at risk for irreversible organ damage [1,9,12,13]. In addition, 30 to 50% of patients experience disease exacerbations [14] (platelet count <150 x 10^9/L after initial recovery and within 30 days of last TPE [15]), which may require rehospitalization and resumption of TPE, and puts patients at risk for thrombotic events and death associated with active disease. aTTP also has a tendency to relapse (recurrent disease >30 days after last TPE[14]) if ADAMTS13 activity is severely deficient [1,4], with relapse rates of ~35 to 40% [6,16] within the first 2 years, each relapse carrying a risk of morbidity and mortality.

Caplacizumab is a bivalent, humanized, single-variable-domain immunoglobulin or Nanobody® targeting the A1 domain of vWF [17], preventing interaction between vWF and platelets, and formation of microvascular thrombi. HERCULES (NCT02553317) was an international phase 3, randomized, double-blind, multicenter, placebo-controlled trial showing that caplacizumab was effective in treating aTTP, significantly shortening the time to normalization of platelet count versus placebo, and reducing the incidence of the composite endpoint (mortality, exacerbations and major thromboembolic events during the treatment period) by 74% and the overall number of TTP exacerbations/relapses by 67% [18]. In HERCULES, caplacizumab had an acceptable safety profile; mild-to-moderate mucocutaneous bleeding was the most frequent treatment-emergent adverse event (TEAE) [18]. Here we report the efficacy and safety outcomes of patients treated with open-label caplacizumab following an exacerbation during the double-blind treatment phase.

2 | METHODS

Detailed methods of the HERCULES study have been published [18]. Briefly, adults with clinically diagnosed aTTP and one prior TPE treatment were randomized to caplacizumab (10 mg intravenous loading dose followed by daily 10 mg subcutaneous doses) or placebo, plus daily TPE and glucocorticoids. Other immunosuppressive therapies were permitted as per local practice. Treatment with caplacizumab continued until 30 days after TPE cessation and could be extended, on a weekly basis (4 weeks maximum), based on the presence of risk factors for recurrence, such as persistent severely deficient ADAMTS13 activity (<10%). The HERCULES trial was conducted in accordance with the principles set out in the Declaration of Helsinki, Good Clinical Practice, and local regulations. All patients provided written, informed consent.

The HERCULES protocol specified that patients who experienced recurrent disease during the treatment period, defined as a new reduction in platelet count necessitating the re-initiation of TPE, were switched to receive open-label caplacizumab plus daily TPE, following the same schedule as the double-blind period (including treatment extension for up to 4 weeks) and maintaining the initial allocation blind. Treatment with caplacizumab beyond this time was not permitted and patients experiencing a second recurrence during open-label therapy were not retreated with open-label caplacizumab and received TPE and appropriate immunosuppression. Assessments, such as ADAMTS13 monitoring were conducted as during the double-blind treatment period, i.e., on a weekly basis following stop of daily TPE, and were used to guide the decision to extend therapy.

Endpoints of interest included time to platelet count response, time to TPE cessation, exacerbations, relapses, major thromboembolic events, and mortality.

3 | RESULTS AND DISCUSSION

Twenty-eight patients in the placebo group and three in the caplacizumab group experienced an exacerbation during the double-blind treatment period (range: 2 to 25 days after daily TPE cessation). Twenty-five of 28 patients in the placebo group had ADAMTS13 activity <10% at the time of exacerbation, indicative of unresolved immunological disease (Table 1). In the

caplacizumab group, all three had an ADAMTS13 activity of <10%. Two patients had an infection likely contributing to the exacerbation, while the third was non-compliant with therapy (Table 1).

Twenty-eight patients restarted daily TPE and received open-label caplacizumab (placebo: n = 26; caplacizumab: n = 2) without breaking the initial-treatment blind; three discontinued study drug treatment upon exacerbation. Of these, 26 patients received corticosteroids during the open-label TPE period. Of these 26, 11 patients also received rituximab (42.3%) during the open-label daily TPE period; this proportion was higher than that seen in the double-blind daily TPE period (12 [17.1%] patients in the caplacizumab arm and 21 [29.6%] patients in the placebo arm), suggesting that investigators were more likely to intensify immunosuppressive therapy after an exacerbation.

The median times from first intravenous injection of study drug to platelet count response (3.49 days) and to daily TPE cessation (6.0 days) in the open-label group (Table 1) were consistent with results of the caplacizumab-treated patients in the randomized phase 2 TITAN study [19] and the double-blind caplacizumab group of the HERCULES study [18].

One patient had an exacerbation while receiving open-label treatment (normal ADAMTS13 activity [60%] and signs of infection), while two others had an exacerbation after prematurely stopping open-label treatment while having low ADAMTS13 activity, hence being at risk for recurrence (reasons for treatment discontinuation: planned splenectomy and serious adverse event [SAE] of dyspnea). A fourth patient relapsed after completion of open-label caplacizumab treatment (Table 1). All three patients who had an exacerbation or relapse after caplacizumab cessation had ADAMTS13 activity <10% at the time of cessation (range of open-label treatment duration: 3 to 65 days; exacerbation/relapse occurred within 8 to 10 days of caplacizumab treatment cessation). This is consistent with relapses observed in the follow-up period after double-blind treatment [18], demonstrating that caplacizumab can protect patients at risk from recurrence and indicating the need to continue treatment with caplacizumab during optimization of immunosuppressive therapy, until resolution of underlying immunological disease is achieved (i.e. partial or complete normalization of ADAMTS13 activity).

One patient experienced an adjudicated major thromboembolic event, vena cava thrombosis, during open-label caplacizumab treatment. Platelet counts at the time of the event were $137x10^9$/L.

The event was considered mild in severity and unrelated to study drug. Treatment was initiated with concomitant heparin (for 2 days) and thereafter enoxaparin sodium, and the event resolved 34 days after onset without interrupting open-label caplacizumab treatment. None of the patients treated with open-label caplacizumab died.

The median duration of exposure to open-label caplacizumab was 36.5 days (range 3 to 65). Twenty-five patients (89.3%) reported at least one TEAE during open-label treatment; most TEAEs were of mild-to-moderate severity (Table 2). Seven patients (25%) had an SAE during open-label treatment (Table 2). Bleeding-related TEAEs were reported in 22 patients (78.6%), the most frequent being catheter site hemorrhage (28.6%), epistaxis (17.9%) and gingival bleeding (14.3%). All bleeding-related TEAEs were of mild-to-moderate severity, and the majority resolved without therapeutic intervention.

Overall, the safety profile of open-label caplacizumab was consistent with that observed in TITAN [19] and in the double-blind period in HERCULES [18]. A similar proportion of patients receiving caplacizumab in the double-blind and open-label periods of HERCULES experienced TEAEs (95.8% vs 89.3%), and mucocutaneous bleeding was a common bleeding-related TEAE in TITAN and both phases of HERCULES [18,19]. Thus, caplacizumab in patients receiving treatment for an exacerbation demonstrated an acceptable safety profile consisting of mainly mild-to-moderate mucocutaneous bleeding, and no new safety signals were identified.

Exacerbations of aTTP not only re-expose patients to the increased risk of morbidity and mortality [16,20], they also lead to readmission and resumption of daily TPE, and its complications [21,22]. Thus, prevention of exacerbations is paramount. In patients who experience an exacerbation, prompt resolution of the episode is required to prevent further complications. Exacerbation rates during the double-blind period of HERCULES was substantially lower in the caplacizumab versus placebo group (4% vs 38%) [18], and was associated with a significant reduction in the need for ongoing TPE and hospitalization. Patients experiencing an exacerbation, mainly from the placebo group, were promptly treated with open-label caplacizumab, and this resulted in similar positive outcomes as seen in the double-blind period of HERCULES, namely a fast normalization of platelet counts, and continued protection against further exacerbations [18]. No patients died during open-label treatment, together with an acceptable safety profile. These results from the open-label phase of HERCULES thus confirm the efficacy and safety of

caplacizumab in controlling platelet consumption and aTTP propagation, even when patients are in an exacerbating state, and demonstrate improved outcomes for aTTP patients.

AUTHOR CONTRIBUTIONS

Flora Peyvandi, Hilde De Winter, and Filip Callewaert designed the research; Paul Knoebl, Spero Cataland, Paul Coppo, Marie Scully, Johanna A. Kremer Hovinga, Ara Metjian, Javier de la Rubia, Katerina Pavenski, performed the research; Flora Peyvandi enrolled patients; Hilde De Winter, and Filip Callewaert were involved in medical monitoring or research overview; Paul Knoebl, Spero Cataland, Flora Peyvandi, Paul Coppo, Marie Scully, Johanna A. Kremer Hovinga, Ara Metjian, Katerina Pavenski, Jessica Minkue Mi Edou, Hilde De Winter, and Filip Callewaert contributed to data analysis/interpretation and reporting. The first draft of this report was prepared by Sheridan Henness, PhD on behalf of Firekite, an Ashfield company, part of UDG Healthcare plc, under direction from the authors. All authors wrote/reviewed the draft manuscript and approved the final version for publication.

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DISCLOSURE OF CONFLICT OF INTEREST

P. Knoebl reports consultancy (advisory board member/speaker fees) from Ablynx/Sanofi, Shire/Takeda, CSL-Behring, Roche and Novo Nordisk, and research funding (unrestricted educational grants) from Novo Nordisk; S. Cataland reports research funding and consulting fees from Ablynx/Sanofi and Alexion; F. Peyvandi reports consultancy for Kedrion, honoraria (speaker at educational meetings) from Ablynx/Sanofi, Grifols, Novo Nordisk, Roche, Shire and Sobi, and has been a member of an advisory board for Ablynx/Sanofi; P. Coppo has been a member of advisory boards for, and receipt of speaker fees from, Ablynx/Sanofi, Alexion and Shire; M. Scully reports advisory boards and speaker fees from Ablynx/Sanofi, Alexion, Shire/Takeda, and Novartis, and research funding from Shire; J. A. Kremer Hovinga reports research funding from Shire and honoraria (to employer, Insel Gruppe AG, Department of Hematology) for participation in advisory boards/presentations from Ablynx/Sanofi, CSL-Behring, Roche, Shire and Siemens;

A. Metjian reports consultancy for Ablynx/Sanofi; J. de la Rubia reports consultancy for Ablynx/Sanofi, AMGEN, Celgene, Janssen, and expert testimony for AMGEN, Celgene and Janssen; K. Pavenski reports research funding (participation in clinical trials) from Ablynx, Bioverativ, Alexion, and Octapharma, and honoraria for participation in advisory boards/presentations from Ablynx, Shire, and Alexion; J. Minkue Mi Edou is employed by Ablynx, a Sanofi company; H. De Winter is employed by Ablynx, a Sanofi company, when this research was conducted; F. Callewaert is employed by Sanofi (formerly employed by Ablynx, a Sanofi company).

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TABLES

Table 1 Patient disposition, baseline characteristics, and efficacy outcomes in patients treated with open-label caplacizumab

Patient disposition	
Experienced an exacerbation (N = 145), n (%)	***31 (21.4%)***
Double-blind placebo group (N = 73)	28 (38.4)
Switched to open-label caplacizumab	*26 (35.6)*
Double-blind caplacizumab group (N = 72)	3 (4.2)
Switched to open-label caplacizumab	*2 (2.8)*
Completed open-label therapy (N = 28), n (%)	***20 (71.4)***
Treatment until 30 days post daily TPE	13 (46.4)
At least one week of treatment extension[a]	7 (25.0)
Premature discontinuations (N = 28), n (%)	***8 (28.6)***
Withdrawal of consent	3 (10.7)
Physician decision	2 (7.1)
Lost to follow up	1 (3.6)
Non-compliance	1 (3.6)
Adverse event	1 (3.6)
Exposure time, median, days (range)	**36.5 (3-65)**
Baseline characteristics at time of exacerbation	**N = 28**
Platelet counts (x10^9/L), mean (range)	
Patients from double-blind placebo group (N = 24)	60.7 (13-149)
Patients from double-blind caplacizumab group (N = 2)	92.5 (71-114)
LDH (U/L), mean (range)	403 (138-1135)
cTnI (µg/L), mean (range)	0.044 (0.010-0.298)
Serum creatinine(µmol/L), mean (range)	100.3 (35-448)
ADAMTS13 activity <10%, n	
Patients from double-blind placebo group (N = 28)	25[b]
Patients from double-blind caplacizumab group (N = 3)	3[c]
Efficacy endpoints	**N = 28**
Median time from first intravenous injection to platelet count response,[d] days (95% CI) [25% percentile, 75% percentile]	3.49 (2.81, 4.81) [2.70, 5.56]
Median time to daily TPE cessation, days (95% CI)	6.0 (5.0, 7.0)

Exacerbation during open-label treatment, n (%)	1 (3.6)[e]
Exacerbation after cessation of open-label treatment, n (%)	2 (7.1)[f]
Relapse after completing open-label treatment, n (%)	1 (3.6)[g]
Deaths, n (%)	0 (0)
Major thromboembolic event, n (%)	1 (3.6)[h]

Abbreviations: CI, confidence interval; cTnI, cardiac troponin I; LDH, lactate dehydrogenase; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura.

[a]In one patient the treatment was extended for 2 weeks, in one patient for 3 weeks, and in five patients for 4 weeks (the maximum treatment extension allowed per protocol).

[b]Of the placebo patients with ADAMTS13 ≥10%, one patient had a reported "suspected drug induced/infection-related TTP exacerbation" (verbatim term), suggestive of an infection-induced thrombocytopenia, and was corroborated by a normal ADAMTS13 of 78% at the time of exacerbation. Two other placebo patients had an ADAMTS13 of 11% and 64%.

[c]In two patients, an infection may have triggered the thrombocytopenia: in one patient the TTP exacerbation was reported as 'Suspected infection associated TTP exacerbation', with an adverse event of 'device-related sepsis (catheter-associated bloodstream infection' reported on the day preceding the exacerbation. The other patient also had findings suggestive of an infection (i.e. increase in C-reactive protein levels and increases in leukocytes and neutrophils). The third patient was non-compliant with therapy while having low ADAMTS13 (patient discontinued at time of exacerbation).

[d]Platelet response defined as an initial platelet count ≥150×10^9/L with subsequent stop of daily TPE within 5 days.

[e]Patient was clinically well and had mild thrombocytopenia at 149 x 10^9/L, while ADAMTS13 activity was normal at 60% and leukocyte and neutrophil counts were mildly elevated, suggestive of subclinical infection. Open-label caplacizumab was permanently withdrawn, as per protocol.

[f]ADAMTS13 activity was <10% at the time of cessation of open-label caplacizumab; treatment was discontinued for a planned splenectomy in one patient (after receiving 3 days of open-label treatment) and for an SAE of dyspnea in another patient (after receiving open-label treatment for the duration of daily TPE and 7 days thereafter).

[g]ADAMTS13 activity was <10% at the time of completion of open-label caplacizumab (therapy was maximally extended for 4 additional weeks, as allowed per protocol)

[h]Vena cava thrombosis (verbatim: “affixing intraluminal thrombotic of posterior wall of inferior cava vein, suspected thrombosis”), considered mild in severity and not related to study drug by the investigator.

Table 2 Overview of treatment-emergent adverse events occurring in patients treated with open-label caplacizumab

	Open-label caplacizumab (n = 28), n (%)
TEAE overview, patients with:	
≥1 TEAE	25 (89.3)
≥1 Serious AE	7 (25.0)
≥1 TEAE leading to death	0
≥1 TEAE leading to study drug withdrawal	1 (3.6)
≥1 TEAE considered at least possibly treatment-related	20 (71.4)
≥1 Serious AE considered at least possibly treatment-related	2 (7.1)
TEAE severity, patients with:	
≥1 Mild TEAE	13 (46.4)
≥1 Moderate TEAE	9 (32.1)
≥1 Severe TEAE	3 (10.7)[a]
Incidence of individual TEAEs	
Serious AEs	
aTTP	4 (14.3)[b]
Upper gastrointestinal hemorrhage	1 (3.6)
Dyspnea	1 (3.6)
Seizure	1 (3.6)
Erythematous rash	1 (3.6)
Most frequent TEAEs (reported in ≥10% of patients)	
Catheter site hemorrhage	8 (28.6)
Headache	6 (21.4)
Epistaxis	5 (17.9)
Gingival bleeding	4 (14.3)
Constipation	4 (14.3)
Diarrhea	4 (14.3)
Abdominal pain upper	4 (14.3)
Rash	4 (14.3)
aTTP	4 (14.3)
Anemia	4 (14.3)
Dyspnea	3 (10.7)

Petechiae	3 (10.7)
Ecchymosis	3 (10.7)
Arthralgia	3 (10.7)

Abbreviations: AE, adverse event; aTTP, acquired thrombotic thrombocytopenic purpura; TEAE, treatment-emergent adverse event.

[a]Severe TEAEs were anemia, dyspnea (temporally related to the removal of the central venous line, and suspected to have been caused by an air embolism and judged unrelated to study drug), and pruritus (judged to be unrelated to study drug and related to therapeutic plasma exchange by the investigator).

[b]One patient experienced recurrence of TTP while receiving open-label treatment; three patients had a recurrence of TTP following cessation of caplacizumab. All three patients had an ADAMTS13 level of <10% at the time of treatment cessation.