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## Long-term follow-up of patients treated with caplacizumab and safety and efficacy of repeat caplacizumab use: Post-HERCULES study

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- Caplacizumab showed efficacy and safety in immune-mediated TTP (iTTP) in the HERCULES trial
- In post-HERCULES, patients with iTTP who completed the HERCULES trial were followed for 3 years
- Caplacizumab during repeated use was efficacious (9 patients) with no new safety signals
- Recurrences were not increased in patients treated in HERCULES with caplacizumab versus placebo

## **Abstract (250/250 words)**

### **Introduction**

Caplacizumab demonstrated efficacy and safety in patients with immune-mediated thrombotic thrombocytopenic purpura (iTTP) in the Phase 3 HERCULES trial. However, data on long-term outcomes following caplacizumab treatment are limited.

### **Objectives**

The post-HERCULES trial (NCT02878603) evaluated long-term outcomes of patients with iTTP treated with caplacizumab in HERCULES and safety and efficacy of repeated caplacizumab use.

### **Patients/Methods**

Over 3 years' follow-up, patients could receive open-label caplacizumab with therapeutic plasma exchange (TPE) and immunosuppressive therapy (IST) in case of recurrence. Adverse events (AEs) were assessed during the overall study period (intention-to-observe [ITO] population) and during recurrences (recurrence population). TTP-related events (TTP-related death, recurrence, major thromboembolic events) were assessed in the efficacy ITO population (patients without recurrence during HERCULES or before post-HERCULES).

### **Results**

Among 104 enrolled patients, incidences of AEs and serious AEs were similar between patients who had received caplacizumab+TPE+IST during HERCULES (n=75) and those treated with placebo+TPE+IST (placebo; n=29). TTP-related events occurred in 8% of patients (4/49) randomized to caplacizumab during HERCULES versus 38% (11/29) randomized to placebo. Nineteen patients had  $\geq 1$  recurrence; 13 of these were treated with caplacizumab. First recurrence episode was resolved or resolving for all patients treated with caplacizumab, including 9 patients with repeat caplacizumab use. All second recurrences (6/6) were resolved. Safety profile of caplacizumab for treatment of recurrence was consistent with HERCULES; most bleeding events were non-serious. No major cases of organ dysfunction were observed.

### **Conclusions**

Long-term follow-up supports the safety and efficacy of caplacizumab for iTTP and its repeated use for recurrences.

**Key words:** Blood platelets, caplacizumab, follow-up studies, thrombotic thrombocytopenic purpura, von Willebrand factor

## 1. INTRODUCTION

Immune-mediated thrombotic thrombocytopenic purpura (iTTP), also known as acquired TTP (aTTP), is a rare, life-threatening hematologic disorder caused by autoantibody-induced deficiency of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), an enzyme that cleaves von Willebrand factor (VWF). [1, 2] iTTP is characterized by severe thrombocytopenia, microangiopathic hemolytic anemia, and tissue ischemia, resulting from accumulation of platelet-adhesive ultra-large VWF multimers and consequent microthrombi formation. [1]

Although iTTP presents as an acute disease, long-term follow-up suggests that recovery from an iTTP episode may often be incomplete. [3] In addition to a 30%–50% risk for relapse, [4-7] survivors of acute iTTP episodes are vulnerable to persistent deficits in physical and cognitive functioning and impaired quality of life. [8, 9] Following complete remission of iTTP, patients are at increased risk for major comorbidities such as depression, hypertension, stroke, chronic renal disease, and autoimmune diseases. [3, 10, 11] Thus, iTTP is associated with long-term consequences on patient health and well-being, highlighting the importance of close follow-up of individuals who have recovered from an acute episode.

Caplacizumab is a bivalent, humanized antibody fragment that targets the A1 domain of VWF, thereby preventing the binding of platelets to ultra-large VWF multimers and inhibiting the formation of microthrombi. [12, 13] In the recent TTP treatment guidelines, the International Society on Thrombosis and Haemostasis (ISTH) panel suggests using caplacizumab over not using caplacizumab for patients with a high pretest probability of TTP and access to ADAMTS13 activity test results within 72 hours. [14] In the Phase 3 HERCULES trial, caplacizumab treatment resulted in significantly faster normalization of platelet count and lower incidence of a composite of TTP-related death, recurrence of iTTP, or thromboembolic event during the treatment period, compared with placebo, among patients with iTTP. [15] The most common adverse event (AE) with caplacizumab was mucocutaneous bleeding, which was mostly mild or moderate. [15] An integrated analysis of the Phase 2 TITAN and Phase 3 HERCULES trials demonstrated a significant reduction in mortality and refractory disease with caplacizumab compared with placebo, with no new safety signals. [16]

The effectiveness of caplacizumab has been evaluated in the real-world setting, and results are in line with clinical trial findings. [17-19] Safety outcomes with caplacizumab in real-world practice were also generally consistent with those from the clinical trials. In the French study, 2 major bleeding events were reported, including hemorrhagic shock with lower digestive tract bleeding and severe

menorrhagia.[17] In the UK study, there were 2 cases of intracranial bleeding with caplacizumab, due to hemorrhagic transformation following extensive cerebral infarction.[18] One major bleeding episode (recurrent vaginal hemorrhages after delivery) was reported with caplacizumab in the German study.[19] While these data provide insight into the effectiveness and safety of caplacizumab in real-world practice, these studies were not conducted in a randomized, controlled setting, and the treatment regimen was heterogenous in the 2 retrospective studies. Furthermore, data on long-term outcomes following caplacizumab treatment are lacking.

We conducted a 3-year prospective follow-up study in patients who completed the HERCULES trial.[15] The objectives of this post-HERCULES study were to: 1) evaluate long-term outcomes of patients treated with caplacizumab; 2) evaluate safety and efficacy of repeated use of caplacizumab in patients experiencing recurrent iTTP; 3) characterize the long-term clinical impact of iTTP.

## 2. METHODS

### 2.1. Study design

Post-HERCULES (NCT02878603) was a multicenter, multinational, prospective, 3-year follow-up study for patients who completed the HERCULES trial per protocol. Details of the HERCULES trial design were described previously. Patients could receive open-label caplacizumab in HERCULES for disease recurrence.[15]

Following completion of HERCULES, patients were invited to attend twice-yearly visits for 3 years, starting with a baseline visit within 1 month after the final 28-day follow-up visit in HERCULES (**Figure S1**). Patients experiencing an iTTP recurrence during the post-HERCULES study period could receive open-label caplacizumab, in conjunction with therapeutic plasma exchange (TPE) and immunosuppression, until 30 days after the last daily TPE. Up to 1 TPE could be given prior to initiation of treatment with caplacizumab, as long as considered part of the TPE for the treatment of the presenting iTTP episode. If ADAMTS13 activity levels remained severely reduced, caplacizumab treatment could be extended for up to a further 28 days. Patients with contraindications to caplacizumab (eg, history of severe hypersensitivity reaction to caplacizumab) or those who met other exclusion criteria (eg, pregnancy) were treated with TPE and immunosuppression. The first patient enrolled in post-HERCULES in October 2016, and the last patient completed the study in October 2020.

In this study, iTTP recurrence was defined as recurrent thrombocytopenia requiring initiation of TPE, including exacerbations (recurrences occurring within 30 days after the last TPE) and relapses (recurrences occurring more than 30 days after the last TPE). New definitions for TTP outcomes have recently been proposed.[20] However, as the post-HERCULES study was conducted prior to the publication of the consensus report, these new definitions were not implemented in the study protocol.

The study protocol was approved by the institutional review board or ethics committee at each site, and the study was conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent.

## **2.2. Assessments**

All patients attended clinic visits at 6-month intervals. Patients experiencing iTTP recurrence had additional visits at time of event, on Day 3 of caplacizumab treatment, then weekly during caplacizumab treatment (starting 1 day after the last daily TPE), and 1 week after the end of caplacizumab treatment. If an exacerbation occurred during an ongoing recurrence assessment period, the visit schedule was restarted.

Assessments at the twice-yearly visits included patient-reported outcome measures, clinical assessments including safety, pharmacodynamic (PD) assessment (VWF antigen [VWF:Ag]), anti-drug antibodies (ADA), and disease-related markers (ADAMTS13 activity and cardiac troponin I [cTnI]). AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. All iTTP recurrences were classified as serious AEs (SAEs). ADAs were determined using a validated screening, confirmatory, and titration ADA bridging assay, with further characterization using the modified ADA (mADA) assay and neutralizing antibody (Nab) assay if required.

During visits after recurrences, assessments included information regarding the iTTP event (treatment, outcome, iTTP duration [defined as initial platelet count  $\geq 150 \times 10^9/L$  with subsequent stop of daily TPE within 5 days], duration of TPE, hospital/intensive care unit days), safety, and pharmacokinetic, ADA, and PD parameters (VWF:Ag and ristocetin cofactor activity), as well as disease-related markers. In patients receiving caplacizumab, treatment-emergent AEs (TEAEs) were assessed from the first administration of caplacizumab up to 30 days after the last administration of caplacizumab.

Cognitive function was assessed at baseline and at study end using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).<sup>21</sup> The total scaled RBANS score is derived from index scores across 5 domains (immediate and delayed memory, attention, language, and visuospatial ability), with a mean of 100 and standard deviation (SD) of 15 (lower scores indicating greater cognitive impairment). Headache burden was assessed at each 6-month visit using the headache impact test (HIT-6™).<sup>22</sup> HIT-6 scores range from 36 to 78, and higher scores indicate greater impact of headaches on daily life and well-being of patients ( $\leq 49$ , little or no impact; 50–55, some impact; 56–59, substantial impact; 60–78, severe impact).<sup>23</sup> Quality of life was measured at each 6-month visit and at the recurrence follow-up visit using the 36-item short-form questionnaire (SF-36).<sup>24</sup> SF-36 scores range from 0 to 100, with higher scores indicating better health status.<sup>25</sup>

### 2.3. Statistical analysis

All analyses were descriptive; no formal statistical testing was performed.

**2.3.1. Analysis populations.** Four different populations were used for analysis (**Figure 1A**):

1. **Overall intention-to-observe (ITO) population (n=104):** All patients enrolled in post-HERCULES.

Safety, pharmacodynamics, disease-related markers, and immunogenicity during the overall study period were assessed in this population. Patients were grouped by those who received caplacizumab during HERCULES (either double-blind or open-label due to iTTP exacerbation) versus those who never received caplacizumab during HERCULES (placebo only).

2. **Efficacy ITO population (n=78; subset of overall ITO population):** Patients in the ITO population who had *not* experienced iTTP exacerbation or relapse during the HERCULES trial or prior to the beginning of post-HERCULES.

TTP-related events (death, recurrence, major thromboembolic event) and patient-reported outcomes were assessed according to randomization in HERCULES (caplacizumab vs placebo); patients were analyzed up to the moment they had an iTTP recurrence. For incidence of TTP-related events, a subanalysis was performed based on rituximab use during HERCULES.

The analysis on the efficacy ITO population was designed to a) show the difference between those randomized to caplacizumab without recurrent disease during HERCULES versus those randomized to placebo in HERCULES who had never received caplacizumab prior to enrollment in post-HERCULES; and b) assess participant evolution in efficacy endpoints while they were recurrence free during post-HERCULES.



**3. Recurrence population (n=19):** All patients in the overall ITO population who experienced  $\geq 1$  iTTP recurrence during post-HERCULES.

Safety and efficacy outcomes during recurrences were analyzed according to whether or not the patient received caplacizumab for the recurrence.

**4. Repeat-use population (n=9; subset of the recurrence population):** Any patients treated at least twice with caplacizumab, because they either received caplacizumab in HERCULES (double-blind or open-label for iTTP exacerbation) and again in post-HERCULES, or treated with caplacizumab for 2 or more recurrent episodes in post-HERCULES.

Safety and immunogenicity during repeated caplacizumab use were assessed in this population.

### 3. RESULTS

#### 3.1. Study population and patient disposition

Of 108 patients who completed the HERCULES trial, 104 elected to enroll in post-HERCULES and constituted the overall ITO population. Among these patients, 75 were treated with caplacizumab during HERCULES (**Figure 1B**; caplacizumab-treated group: 55 were randomized to caplacizumab and 20 were randomized to placebo and treated with open-label caplacizumab for an exacerbation). A total of 29 patients were randomized to placebo and never received caplacizumab during HERCULES (placebo-treated group). Demographics and baseline characteristics were well balanced between the caplacizumab-treated and placebo-treated groups (**Table 1**).

During post-HERCULES, 11/75 patients (15%) in the caplacizumab-treated group and 8/29 patients (28%) in the placebo-treated group experienced  $\geq 1$  recurrence (**Table 2; Figure 2**). Among these 19 patients with  $\geq 1$  recurrence, 18 patients had a relapse and 1 patient had an exacerbation as the first recurrence episode in post-HERCULES. All 6 patients who had a second recurrence in post-HERCULES had relapses as the second recurrence episode.

Of the 19 patients with  $\geq 1$  recurrence, 13 were treated with caplacizumab for  $\geq 1$  recurrence and 6 patients did not receive caplacizumab for any recurrence during post-HERCULES. Reasons for not receiving caplacizumab included pregnancy, patient withdrawal due to neurological deterioration on commencing TPE and transfer to palliative care, investigator's decision (the patient consent form was not yet approved by the institutional review board and therefore the patient could not receive caplacizumab), and receiving  $>1$  TPE before initiation of caplacizumab at recurrence (protocol deviation);

2 patients discontinued the study upon recurrence. One patient with persistently suppressed ADAMTS13 activity (<10% for most visits) had >2 recurrences; this patient experienced 8 recurrences (3 relapses and 5 exacerbations) and was treated with caplacizumab for all events except 1 exacerbation and was included in both analysis groups.

Of 104 enrolled patients, 93 completed the study (**Table 2**). Median follow-up was 1099 days in the caplacizumab-treated group and 1097 days in the placebo-treated group.

### **3.2. Long-term outcomes of patients treated with caplacizumab**

Among patients in the overall ITO population, 68/75 patients (91%) who had been treated with caplacizumab in HERCULES (caplacizumab-treated group) and 26/29 patients (90%) who did not receive caplacizumab during HERCULES (placebo-treated group) had  $\geq 1$  AE during the overall post-HERCULES study period (including events that occurred during and outside of recurrences; **Table 3**). In the caplacizumab-treated group, the most common AEs (excluding TTP) were headache (21%) and investigator-reported decrease in ADAMTS13 activity (17%). At least 1 SAE was reported in 28/75 patients (37%) in the caplacizumab-treated group and 16/29 patients (55%) in the placebo-treated group. Bleeding events occurred in 16/75 patients (21%) in the caplacizumab-treated group and 9/29 patients (31%) in the placebo-treated group. Catheter-site hemorrhage was the most common bleeding event in the caplacizumab-treated group, reported in 3/75 patients (4%).

In the overall ITO population,  $\geq 1$  thromboembolic event was reported in 2/75 patients (3%) in the caplacizumab-treated group (ischemic stroke and transient ischemic attack) and in 3/29 patients (10%) in the placebo-treated group (acute myocardial infarction, venous embolism, and renal infarct).

One patient in the placebo-treated group died as an outcome of iTTP relapse (severe SAE of iTTP). This patient had a history of repeated iTTP episodes and transient ischemic attacks with associated long-standing neurological sequelae. Upon initiating TPE for the recurrent episode, the patient deteriorated further neurologically, and the decision was made against further active treatment; the patient was transferred to a palliative care unit.

In the efficacy ITO population, TTP-related death, recurrence, or  $\geq 1$  treatment-emergent major thrombotic event was reported in 4/49 patients (8%) among those randomized to caplacizumab in HERCULES and in 11/29 patients (38%) among those randomized to placebo (**Table 4**). All recurrences in the efficacy ITO population were relapses. iTTP recurrence occurred in 4/49 patients (8%) randomized to

caplacizumab in the HERCULES trial versus 8/29 patients (28%) randomized to placebo. No patient randomized to caplacizumab in the HERCULES trial had a TTP-related death during post-HERCULES.

**3.2.1. Subgroups by rituximab use in HERCULES (post hoc analysis).** Among the efficacy ITO population, the proportion of patients who had received rituximab during HERCULES was similar between those randomized to caplacizumab (21/49 [43%]) versus those randomized to placebo (12/29 [41%]). Among patients randomized to caplacizumab, recurrences occurred in 10% (2/21) of those with prior rituximab use, versus 7% (2/27) of those who had not used rituximab. In patients randomized to placebo, recurrences occurred in 17% (2/12) of patients with prior rituximab use, versus 35% (6/17) of patients without prior rituximab use (**Table 4**).

**3.2.2. Preemptive rituximab use during post-HERCULES (post hoc analysis).** Preemptive rituximab use was administered at the discretion of the investigators and appeared to be most often employed in the setting of ADAMTS13 <20% detected during routine monitoring as part of the post-HERCULES protocol. In the efficacy ITO population, 11/49 patients (22%) randomized to caplacizumab and 4/29 patients (14%) randomized to placebo were given preemptive rituximab during post-HERCULES in the setting of low ADAMTS13 and normal platelet count ( $>150 \times 10^9/L$ ). None of these patients experienced iTTP relapses.

### **3.3. Safety and efficacy of caplacizumab for the recurrence population during post-HERCULES**

**3.3.1. Concomitant immunosuppressant use during recurrence.** Concomitant rituximab was used for a first recurrence during post-HERCULES in 6/13 patients (46%) treated with caplacizumab and in 3/4 patients (75%) who were not treated with caplacizumab (data were not available for 2 other patients not treated with caplacizumab for recurrence). Concomitant rituximab was used for a second recurrence in 3/6 patients (50%) treated with caplacizumab. All patients received corticosteroids during recurrence. Additional immunosuppressants and other concomitant medications are described in **Table S1**.

**3.3.2. Safety outcomes in the recurrence population treated with caplacizumab (n=13).** Overall, 12/13 patients (92%) treated with caplacizumab for  $\geq 1$  recurrence during post-HERCULES reported  $\geq 1$  TEAE during the first recurrence period; 7/13 (54%) had a TEAE assessed as treatment-related by the investigator (**Table 5**). During the first recurrence period,  $\geq 1$  serious TEAE was reported in 5/13 patients (38%). One patient treated with caplacizumab experienced treatment-related serious TEAEs of hematuria and urinary tract hemorrhage; these events resolved following treatment with factor

VIII/VWF (given once on day of the last hematuria event) and caplacizumab discontinuation. A total of 7/13 patients (54%) experienced  $\geq 1$  bleeding event during the first recurrence period, including epistaxis and intravenous catheter site hemorrhage (n=2 each) and carotid artery perforation, paranasal sinus hemorrhage, hematochezia, hemorrhoidal hemorrhage, hematuria, urinary tract hemorrhage, menorrhagia, and contusion (n=1 each). Five hypersensitivity reactions were reported in 3/13 patients (23%) treated with caplacizumab. Two events (injection site reactions) occurring in the same patient were considered related to caplacizumab. Both events were mild and resolved without treatment interruption.

Of 6 patients treated with caplacizumab for a second recurrence during post-HERCULES, 5 (83%) reported  $\geq 1$  TEAE; 2 (33%) had  $\geq 1$  bleeding event (gastrointestinal hemorrhage and intravenous catheter site hemorrhage). One treatment-related serious TEAE of gastrointestinal hemorrhage event was reported with caplacizumab treatment for a second recurrence. The patient required hospitalization but did not require reversal with factor VIII/VWF or interruption of caplacizumab therapy.

No major thromboembolic events were reported for any patient with a recurrence during post-HERCULES.

**3.3.3. Efficacy outcomes for the recurrence population.** For first recurrences in post-HERCULES, all episodes were considered resolved (12/13) or resolving (1/13) in patients who received caplacizumab for the recurrence. Among 6 patients who did not receive caplacizumab for the first recurrence, the episode was considered resolved for 4/6 patients (67%); 1 patient died as an outcome of the recurrence (this patient did not receive caplacizumab either during HERCULES or post-HERCULES), and the outcome was not reported for 1 patient. All second recurrences (all treated with caplacizumab) resolved (6/6).

Duration of iTTP was reported by the investigator and defined as achieving platelet count  $\geq 150 \times 10^9/L$  with subsequent stop of daily TPE within 5 days. Among patients experiencing their first iTTP recurrence during post-HERCULES, the median (range) *duration of the episode* was 7 days (3–24 days) for patients treated with caplacizumab and 10 days (5–15 days) for those not treated with caplacizumab (**Table S2**). All patients received caplacizumab for their second recurrence during post-HERCULES; median (range) duration of the second recurrence was 5.5 days (3–6 days). The median (range) *duration of caplacizumab treatment* was 56 days (17–71 days) for the first recurrence and 56 days (33–63 days) for the second recurrence.

Median (range) *duration of TPE* for the first recurrence was 5 days (2–9 days) for patients treated with caplacizumab and 5.5 days (4–7 days) for those not treated with caplacizumab. Median (range) *number of days in the hospital* was 7 days (4–23 days) and 10 days (9–11 days), respectively. (Table S2).

### 3.4. Safety and immunogenicity during repeat caplacizumab use (n=9)

Of 13 patients treated with caplacizumab for recurrent iTTP during post-HERCULES, 9 received repeated administration of caplacizumab. Of these 9 patients, 4 had been randomized to caplacizumab in HERCULES, 4 had received open-label caplacizumab for an exacerbation during HERCULES, and 1 had been randomized to placebo in HERCULES and received caplacizumab twice for 2 recurrences during post-HERCULES. All first and second recurrences during post-HERCULES were resolved for patients with repeat caplacizumab use.

Among the 9 patients with repeated caplacizumab administration, 4 patients (44%) had  $\geq 1$  serious TEAE during the first recurrence period (Table 5). A total of 7 patients experienced treatment-emergent bleeding events during repeated caplacizumab administration (for first or subsequent recurrence during post-HERCULES). Among these, 2 patients had  $\geq 1$  serious treatment-emergent bleeding event (urinary tract hemorrhage/hematuria in 1 patient, gastrointestinal hemorrhage in another, described in 3.3.2); 6 patients had  $\geq 1$  non-serious treatment-emergent bleeding event.

Two patients with repeat caplacizumab use had treatment-emergent ADAs positive in a functional Nab assay. No apparent influence of treatment-emergent ADAs on ristocetin cofactor activity or change from baseline in VWF:Ag concentration was found.

### 3.5. Long-term clinical impact of iTTP

**3.5.1. Organ damage markers (overall ITO population).** In the overall ITO population (Figure 1A), no elevations in cTnI were observed at baseline, nor were any trends over time noted throughout the study for either group. cTnI values were  $< 0.5 \mu\text{g/L}$  for all patients with cTnI measurements at every follow-up, except for 1 patient with cTnI  $0.727 \mu\text{g/L}$  at the 30-month follow-up. Lactate dehydrogenase (LDH) and serum creatinine values at baseline were within the normal range for the majority of patients in the overall ITO population (83% [86/104] and 88% [92/104], respectively), and no clinically significant changes were observed during the study period. An AE of increased serum creatinine at any time during the study was reported in 2/75 patients (3%) in the caplacizumab-treated group.

**3.5.2. Cognitive function and quality of life outcomes (efficacy ITO population).** Mean baseline RBANS total scores were similar between treatment groups in the efficacy ITO population (Figure 1A).

Numerically greater improvement from baseline to 3-year follow-up was observed in patients randomized to caplacizumab versus placebo (mean difference was 4.2 vs 2.1, respectively; **Table S3**). No clinically meaningful difference (minimally clinically important difference = 8)[26] was observed between groups in the improvement of RBANS score.

Mean (SD) HIT-6 scores were 48.2 (9.9) at baseline and 49.4 (10.2) at the 3-year follow-up in patients randomized to caplacizumab; mean scores were 45.0 (10.0) and 44.4 (10.1), respectively, in patients randomized to placebo (**Figure S2**). Mean SF-36 scores were similar between groups and remained stable over time (**Table S4, Figure S3**).

## 4. Discussion

In this 3-year follow-up study of the HERCULES trial, the safety profile of patients exposed to caplacizumab in conjunction with TPE and immunosuppression appeared similar to those who had received TPE and immunosuppression only. Incidence of iTTP-related events, including recurrences, was not increased in patients who received caplacizumab versus placebo in HERCULES. Moreover, no new safety concerns or boosting of ADA responses were observed with repeat administration of caplacizumab. All first and second recurrences treated with caplacizumab during the study period were resolved or resolving, including those with repeat caplacizumab use.

Despite complete remission, up to 50% of patients who have survived an iTTP episode remain at risk for relapse.[27] In the Phase 2 TITAN trial in patients with iTTP, although caplacizumab treatment led to lower rates of exacerbation, relapse rates during the 1-month follow-up period were higher in patients treated with caplacizumab versus placebo.[28] Patients who experienced a relapse during the TITAN trial had persistently low ADAMTS13 activity (<10%), indicating incomplete resolution of the underlying autoimmune activity. Indeed, compared with the TITAN trial, relapse rates with caplacizumab were lower in the Phase 3 HERCULES trial, in which patients with persistent ADAMTS13 deficiency were allowed to extend their caplacizumab treatment beyond 30 days after the end of TPE, together with optimization of immunosuppression (eg, rituximab).[15] During this 3-year follow-up, there was no observed increase in the incidence of iTTP relapses or exacerbations in patients who had initially received caplacizumab (15%) or placebo (28%) in the HERCULES trial. Moreover, there was a general trend towards fewer TTP-related events with caplacizumab versus placebo, and resolution of TTP episodes with caplacizumab occurred within approximately 5 days.

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Although the role of rituximab was not a pre-stated goal of this study, we investigated the potential contribution of rituximab use to recurrence rates. Rituximab, when used during an acute iTTP episode or preemptively in clinical remission, has been shown to prevent relapses.[29, 30] In post-HERCULES, among patients randomized to placebo in HERCULES (and who did not have an exacerbation during HERCULES), the rate of recurrence was lower in patients who received rituximab in HERCULES (17%) versus those who had not (35%). However, among patients randomized to caplacizumab, recurrence rates were similar regardless of prior rituximab use. As prior rituximab use in HERCULES was similar in both groups (43% in the caplacizumab group vs 41% in the placebo group), it is possible that the recurrence rate of 8% among patients randomized to caplacizumab versus 28% in those randomized to placebo was influenced by the higher proportion of prophylactic rituximab use in the caplacizumab group (22%) compared with the placebo group (14%) during post-HERCULES. Previous studies have demonstrated that prophylactic rituximab during iTTP remission in patients with low ADAMTS13 levels improves relapse-free survival.[31, 32] Indeed, in post-HERCULES, all patients who received preemptive rituximab were relapse-free during the follow-up period.

Post-HERCULES is the first study to assess the safety and efficacy of repeated caplacizumab use for iTTP recurrence. The safety profile of caplacizumab during repeated use was similar to that observed in the TITAN and HERCULES clinical trials and in real-world studies,[17-19] with no new safety concerns. In line with previous studies and with its mechanism of action, caplacizumab during its repeat use was associated with bleeding risk; however, most bleeding events were non-serious. No major thromboembolic events or TTP-related deaths were reported with repeated caplacizumab use. The relationship and timing between some AEs, such as headache, and TTP relapses, and the long-term impact of ADAs in patients treated with caplacizumab, warrant evaluation in the future.

iTTP is associated with long-term consequences, such as long-term deficits in health-related quality of life in patients following acute iTTP episodes, and potential for persistent organ damage.[3, 8, 10] Due to small sample sizes at each 6-month follow-up visit in the post-HERCULES study, limited conclusions can be drawn regarding the long-term clinical impact of iTTP on cognition and quality of life. However, descriptive analyses indicate that cognitive functioning and quality-of-life measures were stable or improved slightly over time during 3-year follow-up both in patients who had received caplacizumab and those who did not. Over 3 years' follow-up, no major cases of organ dysfunction were observed; markers of organ damage, including cTnI, creatinine, and LDH, were in the normal range for almost all patients.

In addition to small sample sizes, a limitation of this study is the complex heterogeneity of the treatment course in the study population. Patients in post-HERCULES may have received caplacizumab in HERCULES due to randomization or due to switch to open-label caplacizumab for treatment of recurrences in those randomized to placebo during HERCULES. Also, duration of caplacizumab exposure was variable, and the race distribution of the study population differed from the TTP race distribution in the United States.[33]

Overall, these data demonstrate that over long-term follow-up, caplacizumab, including its repeated administration, appeared safe and effective for the treatment of iTTP. Based on its mechanism of action, caplacizumab is not expected to affect the underlying autoimmune activity in iTTP. Nevertheless, the incidence of recurrences in patients treated with caplacizumab was not higher than in those treated with TPE and immunosuppression alone. These results further support the role of caplacizumab, when administered with TPE and immunosuppression, for initial and relapsing iTTP episodes and demonstrate its safety and effectiveness during retreatment. Real-world evidence from ongoing iTTP registry studies is needed to assess long-term outcomes with caplacizumab in clinical practice.



## Author contributions

M. Scully, J. de la Rubia, K. Pavenski, A. Metjian, P. Knöbl, F. Peyvandi, S. Cataland, P Coppo, and J.A. Kremer Hovinga designed or performed the research and contributed to analysis and interpretation of results.

J. Minkue Mi Edou contributed to data analysis/interpretation and reviewed the paper.

R. De Passos Sousa, F. Callewaert, S. Gunawardena, and J. Lin overviewed research during the study and analyzed and interpreted data.

All authors wrote/reviewed the draft manuscript and approved the final version for publication.

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## Conflicts of interest

**MS** has provided consultancy at advisory boards and received speaker fees from Ablynx/Sanofi, Shire/Takeda, and Novartis, and research funding from Shire. **JDLR** has provided consultancy at Ablynx/Sanofi, Amgen, Celgene, and Janssen, and expert testimony at Amgen, Celgene, and Janssen. **KP** participated in studies of Ablynx/Sanofi, Bioverativ/Sanofi, Alexion, Shire/Takeda, and has received honoraria for speaking and consulting from Ablynx/Sanofi, Bioverativ/Sanofi, Shire/Takeda, Alexion, and Pfizer. **AM** has provided consultancy for Ablynx/Sanofi. **PK** is a member of advisory boards and has received speaker fees from Ablynx/Sanofi, Shire/Takeda, CSL Behring, Roche, and Novo Nordisk, and has received research grants from Novo Nordisk. **FP** is a speaker at educational meetings for Bioverativ, Grifols, Roche, Sanofi, Sobi, Spark, and Takeda, and a member of advisory boards for Roche, Sanofi, and Sobi. **SC** has provided consultancy for and received research funding from Ablynx/Sanofi and Alexion. **PC** is a member of advisory boards for and received speaker fees from Ablynx/Sanofi, Alexion, and Shire. **JAKH** is a member of advisory boards for Ablynx/Sanofi and Takeda; has received research grants from Baxter, now part of Takeda; and has been a speaker at symposia for Ablynx/Sanofi, CSL Behring, Roche,

and Siemens. **SG** and **JL** are employees of Sanofi and may hold shares and/or stock options in the company. **JMME**, **FC**, and **RDPS** are former employees of Sanofi and may hold shares and/or stock options in the company.

#### **Data sharing statement**

Qualified researchers may request access to patient-level data and related study documents, which may include clinical study report, study protocol with any amendments, statistical analysis plan, and dataset specifications. Patient-level data are anonymized. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: <https://www.vivli.org/>.

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**Figure 1. Post-HERCULES (A) populations and analysis groups and (B) patient flow chart**

IST, immunosuppressive therapy; ITO, intention-to-observe; iTTP, immune-mediated thrombotic thrombocytopenic purpura; OL, open-label; TPE, therapeutic plasma exchange.

<sup>a</sup>One patient had multiple relapses and exacerbations (recurrences) and was treated for all except 1. Thus, this patient appears in both “not treated with caplacizumab” and “treated with caplacizumab.” <sup>b</sup>Two patients had an exacerbation during double-blind caplacizumab, and switched to OL caplacizumab, but were exposed to caplacizumab only.

**Figure 2. Flowchart of patients with recurrences during post-HERCULES**

IST, immunosuppressive therapy; TPE, therapeutic plasma exchange.

**Table 1. Demographics and patient characteristics at baseline**

<b>Overall ITO population</b>	<b>Caplacizumab-treated group in HERCULES (n=75)</b>	<b>Placebo-treated group in HERCULES (n=29)</b>
Age, median (range)	45 (23–77)	48 (23–80)
Female, n (%)	51 (68)	23 (79)
Race, n (%)		
White	52 (69)	21 (72)
Black	13 (17)	6 (21)
Asian	3 (4)	0
Other	2 (2.7)	0
Data missing	5 (7)	2 (7)
Weight, mean (SD), kg	86.4 (20.9)	85.6 (30.1)
Height, mean (SD), cm	167.7 (8.8)	166.0 (10.7)
ADAMTS13 activity (%), mean (SD)	60.5 (35.7)	66.5 (41.0) <sup>a</sup>

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ITO, intention-to-observe; SD, standard deviation.

<sup>a</sup>n=28.



**Table 2. Patient disposition during post-HERCULES**

<b>Overall ITO population; n (%)</b>	<b>Caplacizumab-treated group in HERCULES (n=75)</b>	<b>Placebo-treated group in HERCULES (n=29)</b>
≥1 TTP recurrence	11 (15)	8 (28)
≥1 TTP recurrence and treated with caplacizumab	8 (11)	5 (17)
≥1 TTP recurrence and not treated with caplacizumab <sup>a</sup>	3 (4)	3 (10)
Completed the study period	70 (93)	23 (79)
Reasons for discontinuation		
Lost to follow-up	1 (1)	4 (14)
Withdrawal by subject	1 (1)	1 (3)
Death	0	1 (3)
Physician's decision	3 (4)	0

For patients who discontinued the study, no censoring or exclusion of the patient was applied.

ICF, informed consent form; IRB, institutional review board; ITO, intention-to-observe; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura.

<sup>a</sup>Of the 6 patients who did not receive caplacizumab for recurrence during post-HERCULES, 2 discontinued the study upon the recurrence event. Reasons for not receiving caplacizumab included pregnancy, investigator's decision due to pending IRB approval for latest ICF, patient withdrawal due to neurological deterioration on commencing TPE and transferred to palliative care, receiving more than 1 TPE before initiation of caplacizumab at recurrence.

**Table 3. AEs during overall study period**

Overall ITO population, n (%)	Caplacizumab-treated group in HERCULES (n=75)	Placebo-treated group in HERCULES (n=29)
≥1 AE	68 (91)	26 (90)
AE reported in ≥15% in either group (PT)		
Headache	16 (21)	9 (31)
TTP	11 (15)	8 (28)
Nasopharyngitis	6 (8)	6 (21)
Diarrhea	5 (7)	5 (17)
Paresthesia	4 (5)	5 (17)
ADAMTS13 activity decreased <sup>a</sup>	13 (17)	0 (0)
≥1 SAE	28 (37)	16 (55)
≥1 bleeding event <sup>b</sup>	16 (21)	9 (31)
≥1 AE leading to death	0	1 (3)
≥1 thromboembolic event	2 (3)	3 (10)
Ischaemic stroke	1 (1.3)	0
Transient ischaemic attack	1 (1.3)	0
Acute myocardial infarction	0	1 (3.4)
Venous embolism	0	1 (3.4)
Renal infarct	0	1 (3.4)

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; AE, adverse event; ITO, intention-to-observe; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAE, serious adverse event; TTP, thrombotic thrombocytopenic purpura.

<sup>a</sup>Based on investigator reporting. <sup>b</sup>Based on Standardized MedDRA Query, with exclusion of TTP.

**Table 4. TTP-related events during the post-HERCULES study period according to randomization in the HERCULES study**

Efficacy ITO population, n (%)	All patients		Patients without rituximab use in HERCULES		Patients with rituximab use in HERCULES	
	Randomized to caplacizumab (n=49)	Randomized to placebo (n=29)	Randomized to caplacizumab (n=28)	Randomized to placebo (n=17)	Randomized to caplacizumab (n=21)	Randomized to placebo (n=12)
TTP-related events	4 (8)	11 (38)	2 (7)	8 (47)	2 (10)	3 (25)
TTP-related death <sup>a</sup>	0	1 (3)	0	1 (6)	0	0
Recurrence of TTP	4 (8)	8 (28)	2 (7)	6 (35)	2 (10)	2 (17)
≥1 major TE event (excluding TTP)	0	3 (10)	0	2 (12)	0	1 (8)

ITO, intention-to-observe; TE, thromboembolic event; TTP, thrombotic thrombocytopenic purpura.

<sup>a</sup>A patient who never received caplacizumab died after having a TTP recurrence.

**Table 5. TEAEs in patients treated with caplacizumab for recurrence in post-HERCULES**

<b>Patients with events during first recurrence period in post-HERCULES, n (%)</b>	<b>Treated with caplacizumab in post-HERCULES (n=13)</b>	<b>Repeat caplacizumab use (n=9)</b>
≥1 TEAE	12 (92)	8 (89)
≥1 TEAE occurring in ≥15% of patients in either group		
TTP	3 (23)	2 (22)
Headache	3 (23)	1 (11)
Constipation	3 (23)	3 (33)
Nausea	2 (15)	1 (11)
Vomiting	2 (15)	2 (22)
Epistaxis	2 (15)	2 (22)
Catheter site hemorrhage	2 (15)	1 (11)
Injection site pain	2 (15)	2 (22)
Pruritis	2 (15)	2 (22)
Hypokalemia	2 (15)	2 (22)
≥1 treatment-related TEAE	7 (54)	6 (67)
≥1 serious TEAE	5 (38)	4 (44)
TTP	3 (23)	2 (22)
Hematuria	1 (8)	1 (11)
Urinary tract hemorrhage	1 (8)	1 (11)
Allergic transfusion reaction	1 (8)	1 (11)
≥1 treatment-related serious TEAE	1 (8)	1 (11)
≥1 TEAE leading to death	0	0
≥1 TEAE leading to study drug interruption	2 (15)	2 (22)
≥1 TEAE leading to study drug withdrawal	1 (8)	1 (11)
TEAE of special interest		
≥1 bleeding event	7 (54) <sup>a</sup>	5 (56)
≥1 thromboembolic event	0	0
≥1 hypersensitivity reaction	3 (23)	2 (22)
≥1 treatment-related hypersensitivity reaction	1 (8)	1 (11)

MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; TTP, thrombotic thrombocytopenic purpura.

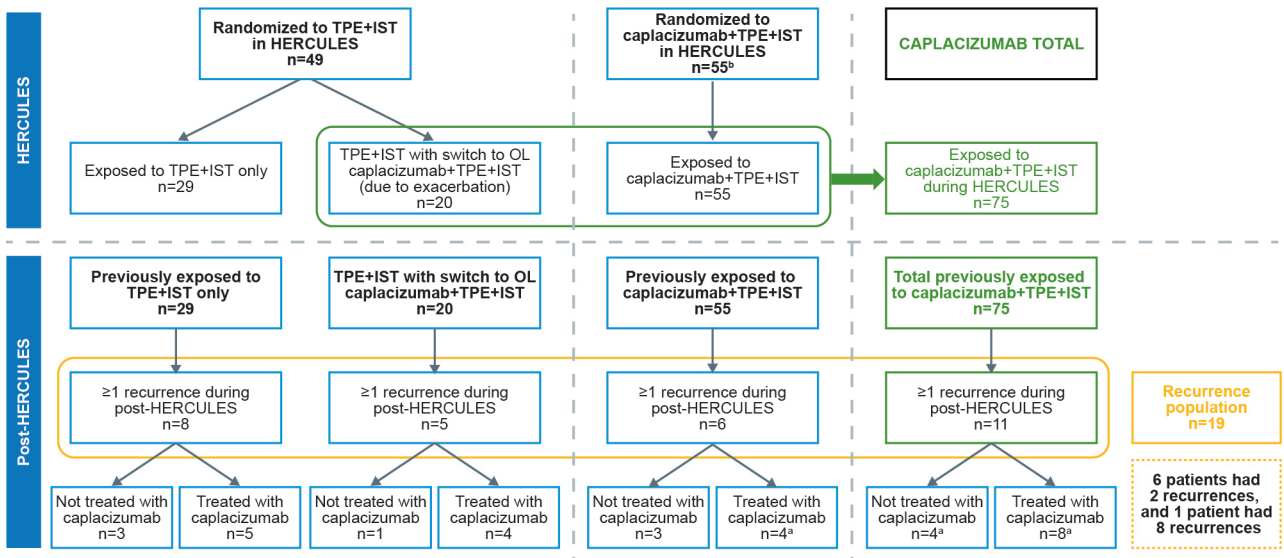
<sup>a</sup>Based on Standardized MedDRA Query, with exclusion of TTP.

A

Populations	Analysis groups
<b>Overall ITO Population (n=104):</b> All enrolled patients in post-HERCULES	Treated with TPE+IST in HERCULES (n=29) versus treated with caplacizumab+TPE+IST in HERCULES (n=75)
<b>Efficacy ITO Population (n=78):</b> Patients in the ITO population without iTTP recurrence in HERCULES or prior to the beginning of post-HERCULES	Randomized to TPE+IST in HERCULES (n=29) versus randomized to caplacizumab+TPE+IST in HERCULES (n=49)
<b>Recurrence Population (n=19):</b> Patients in the ITO population with $\geq 1$ recurrence in post-HERCULES	Not treated with caplacizumab in post-HERCULES (n=7) <sup>a</sup> versus treated with caplacizumab in post-HERCULES (n=13)
<b>Repeat Use Population (n=9):</b> Patients treated at least twice with caplacizumab, because they 1) received caplacizumab in HERCULES and were treated again in post-HERCULES, or 2) were treated at least twice in post-HERCULES	

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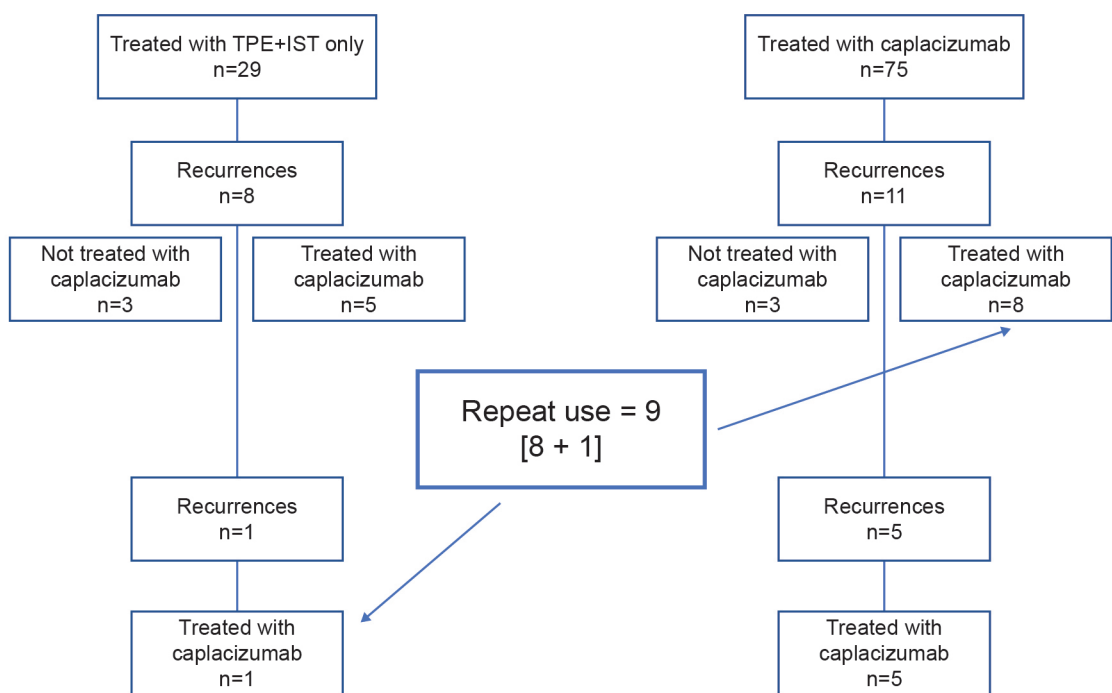
B



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Recurrence 1

Recurrence 2



One patient in the caplacizumab-treated group had 8 recurrences; this patient was treated with caplacizumab for all recurrences except for recurrence 6

JTH\_15892\_SAN [21791] Figure 2.jpg