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ORIGINAL ARTICLE

Caplacizumab improves clinical outcomes and is well tolerated across clinically relevant subgroups of patients with immune-mediated thrombotic thrombocytopenic purpura

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Abstract

Background: Immune-mediated thrombotic thrombocytopenic purpura (iTTP) may lead to microvascular thrombosis and mortality, despite patients receiving appropriate standard of care treatment (immunosuppressive therapy and therapeutic plasma exchange). Caplacizumab directly inhibits von Willebrand factor–platelet interaction and consequently prevents microthrombi formation.

Objectives: This study aimed to determine the efficacy and safety of caplacizumab in diverse, clinically relevant patient subgroups.

Methods: In this post hoc analysis of phase 3 HERCULES study (NCT02553317), patients were categorized by clinically relevant subgroups (prior iTTP history, iTTP severity at presentation, and initial immunosuppression regimen).

Results: In patients with previous acute iTTP episodes, less severe disease at presentation, or those who received a corticosteroid-only initial immunosuppression regimen, time to platelet count response was shorter with caplacizumab vs placebo. Across all subgroups, fewer patients experienced a composite outcome of iTTP-related death, exacerbation, or major thromboembolic event on caplacizumab vs placebo. Placebo-treated patients remained at risk of exacerbations and refractoriness on either initial immunosuppression regimen (ie, corticosteroids only or corticosteroids plus rituximab). In the corticosteroids plus rituximab group, no exacerbations were reported in caplacizumab-treated patients, but 8 of the 16 (50%) patients experienced exacerbations in the placebo group. Safety outcomes were consistent with the findings of the main HERCULES study.

Conclusion: Caplacizumab treatment of acute iTTP, in combination with therapeutic plasma exchange and immunosuppression, was safe and effective regardless of prior iTTP history, severity, or initial immunosuppression regimen and improved patient outcomes across clinically diverse subgroups. These findings emphasize the need for treatments with rapid onset of action that can reduce mortality and iTTP-related complications.

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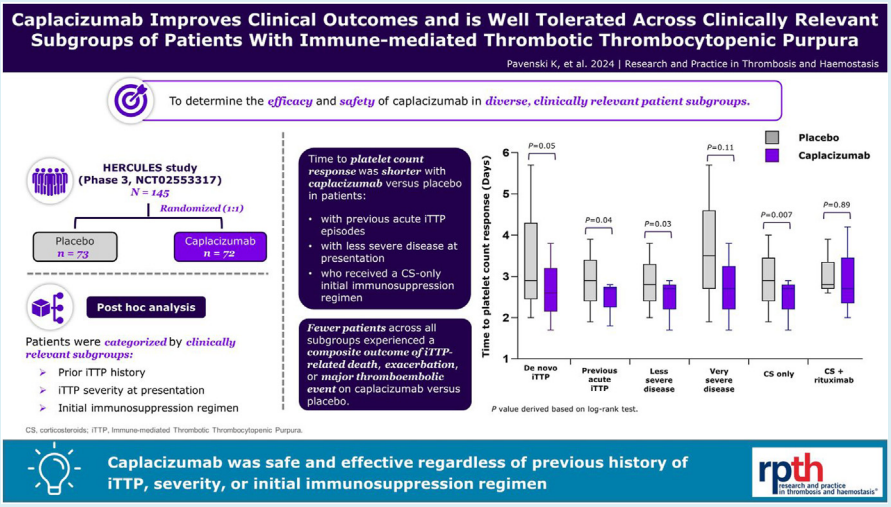


KEYWORDS
caplacizumab, efficacy, prognosis, thrombotic thrombocytopenic purpura, treatment outcome

Essentials

- Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a life-threatening disease.
- Despite standard treatment, some patients still experience poor outcomes.
- Caplacizumab with standard treatment improved outcomes across clinically diverse subgroups.
- Caplacizumab should be initiated rapidly in all patients with acute iTTP.

1 | INTRODUCTION

Immune-mediated thrombotic thrombocytopenic purpura (iTTP), also known as acquired thrombotic thrombocytopenic purpura, is a rare, life-threatening thrombotic microangiopathy caused by autoantibody-mediated deficiency in the activity of the von Willebrand factor (VWF)-cleaving enzyme ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) [1,2]. In iTTP, formation of platelet-rich microthrombi in the microvasculature leads to thrombocytopenia, microangiopathic hemolytic anemia, and tissue ischemia with consequent multiorgan damage of variable severity [1,2]. Despite treatment with therapeutic plasma exchange (TPE) and immunosuppression, patients still experience poor outcomes including refractoriness, exacerbation, and death; patients who survive acute iTTP episodes remain at risk of relapse with an increased risk of mortality and morbidity in the long term [3–6]. Consequently, there has been a focus on developing therapies with rapid onset of action that can reduce early mortality and refractoriness and improve longer-term clinical outcomes [7].

Caplacizumab directly targets the pathologic microthrombi formation that occurs in iTTP by inhibiting von Willebrand factor–platelet interaction and therefore has the potential to improve outcomes in the acute phase of the disease [8,9]. The efficacy and safety of caplacizumab for the treatment of iTTP have been established in phase 2 TITAN and phase 3 HERCULES clinical trials [10,11]. Furthermore, an integrated analysis of these trials has demonstrated that caplacizumab can prevent mortality and refractoriness [12].

While real-world studies support the benefit of early caplacizumab in iTTP [13–16], some unanswered questions remain regarding optimizing iTTP management: 1) Is caplacizumab potentially beneficial to all patients with acute iTTP, regardless of their clinical presentation, or should patients be stratified by their disease severity or TTP history to guide treatment decisions? 2) Does the initial concomitant immunosuppression regimen impact the efficacy of caplacizumab?

We performed a series of post hoc analyses of data from the HERCULES study (NCT02553317) to determine the efficacy and safety of caplacizumab in diverse, clinically relevant patient subgroups.

2 | METHODS

The HERCULES 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.

2.1 | Study design

Full study details of phase 3, double-blind, placebo-controlled HERCULES trial (NCT02553317) have been reported previously [11]. Briefly, 145 patients with an acute episode of clinically diagnosed iTTP were randomized 1:1 to receive caplacizumab (n = 72) or placebo (n = 73), in conjunction with TPE and immunosuppression, until 30 days after the last TPE. It should be noted that severe ADAMTS13 deficiency was not an eligibility criterion; however, ADAMTS13 testing was conducted at the start of the TPE period and at weekly intervals during the 30-day post-TPE period. For patients with persistent deficiency of ADAMTS13 (assessed weekly), treatment was allowed to be extended for up to 28 days together with optimization of immunosuppression. Patients who experienced exacerbations during the double-blind treatment period were switched to open-label caplacizumab together with reinitiation of TPE. All patients provided informed consent before enrollment. A series of post hoc subgroup analyses were performed in the HERCULES study population, based on clinically relevant characteristics.

2.2 | Efficacy outcomes in clinically relevant subgroups

For post hoc analysis, clinically relevant subgroups were categorized according to the following characteristics: prior iTTP history, iTTP severity at presentation, and initial immunosuppression regimen. To group by prior iTTP history, patients participating in HERCULES were categorized according to whether they had de novo iTTP or previous acute iTTP episodes. For iTTP severity at presentation, patients were stratified into less severe or very severe disease subgroups. Very severe disease at presentation was defined as French severity score of ≥3 (score assesses presence of cerebral involvement, lactate dehydrogenase [LDH] >10 × upper limit of normal [ULN] and age [≤40/>40 to ≤60/>60 years] [17]), or severe neurologic involvement (measured by Glasgow coma scale score of ≤12 [severe] or 13-15 [nonsevere]; score assesses aspects of best eye response, verbal response, and motor response, with lower scores indicating worse function [18]), or cardiac involvement (cardiac troponin I >2.5 × ULN). Assessment as severe/very severe as per any one of these criteria was sufficient for inclusion in the very severe subgroup. Patients in the HERCULES study population were also stratified based on the initial immunosuppressive regimen received. Initial immunosuppression regimen was defined as therapy that was started up to day 3 of the treatment period. Treatment with high-dose corticosteroids was mandated by the study protocol, and other immunosuppressive therapy was permitted in accordance with clinical practice at each site [11]. For all patients, corticosteroid treatment had to be initiated/continued with a prednisolone or prednisone regimen of at least 1 mg/kg/d intravenously or orally during the daily TPE period and continued for the first week after the end of daily TPE. Afterward, corticosteroids could be tapered at the discretion of the investigator, with the aim of being corticosteroid free by day 30 after cessation of daily TPE as clinically indicated. The main 2 groups analyzed were those who received corticosteroids only and those who received a combined regimen of corticosteroids and rituximab during the frontline period (up to day 3 of treatment or screening phase). Other immunosuppressive agents such as mycophenolate mofetil or cyclosporine were not included in the analysis. Differences in dose or dosing frequency of immunosuppressive therapy were not taken into consideration in this descriptive analysis. However, descriptive data on corticosteroid dose by immunosuppression treatment group are provided in Supplementary Table S1.

Efficacy outcomes in these subgroups were as reported previously for HERCULES [11] and included the following: time to platelet count response, defined as time to initial platelet count of ≥150 $\times 10^9$/L with subsequent stop of daily TPE within 5 days; composite of iTTP-related death, exacerbation of iTTP, or at least 1 treatment-emergent major thromboembolic (TE) event during the blinded treatment period; and refractory iTTP, defined as absence of a doubling of the platelet count after 4 days of treatment and an LDH level that remained above the ULN. An iTTP exacerbation was defined if, after initial recovery, a new decrease in platelet count was observed ≤30 days after last TPE, whereas a relapse was defined if this occurred >30 days after stopping TPE. Following an exacerbation, patients were required to restart daily TPE, intensify immunosuppression, and move to open-label caplacizumab, whereas following relapse, patients were required to restart daily TPE and immunosuppression only. Recurrence was defined as the occurrence of either an exacerbation or relapse. Sustained ADAMTS13 activity of ≥20% was defined as 2 consecutive ADAMTS13 levels of ≥20%, where ADAMTS13 levels were measured at baseline and weekly from time of stopping TPE.

2.3 | Safety outcomes in clinically relevant subgroups

Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) were summarized and are described for each subgroup.

2.4 | Statistical analysis

Data on time to platelet count normalization and time to recurrence (ie, exacerbation or relapse) were analyzed by subgroups (prior iTTP history, disease severity at presentation, and initial immunosuppression regimen) using a Cox proportional hazards regression model, with time to platelet count response or time to recurrence as dependent

variables and treatment group and Glasgow coma scale category as independent variables. The hazard ratio (HR) from the Cox model is reported with 95% CIs. No other formal statistical testing was conducted due to the post hoc nature of the analyses, and all data are presented descriptively.

3 | RESULTS

3.1 | Efficacy outcomes in clinically relevant subgroups

3.1.1 | Prior iTTP history

At baseline, of the 145 patients enrolled in HERCULES, 82 (56.6%) had de novo iTTP and 63 (43.4%) had previous acute iTTP episodes (Table 1). Of those who received caplacizumab, 48 of the 72 (66.7%) presented with de novo iTTP compared with 34 of the 73 patients (46.6%) in the placebo group (Table 2). Demographic characteristics and duration of follow-up were generally balanced between the 2 prior iTTP history subgroups (Table 1). In the subgroup of patients with de novo iTTP, the median (Q1, Q3) age was 45.5 (37.0, 58.0) years and 68.3% were female, while those who had previous acute iTTP episodes had a median (Q1, Q3) age of 43.0 (35.0, 55.0) years and 69.8% were female. In patients with de novo iTTP, there was a trend toward delayed presentation, with a median (Q1, Q3) time from first symptom until diagnosis of 4.0 (1.0, 7.0) days in this subgroup compared with 2.0 (1.0, 4.0) days in those who had experienced previous acute iTTP episodes. A lower mean (SD) baseline platelet count was observed in the de novo episode subgroup (28.8×10^9/L [22.3]) compared with those with previous episodes (44.4×10^9/L [32.8]) (Table 1).

In patients with de novo iTTP, median (95% CI) time to platelet count response was 2.6 days (1.8, 2.9) with caplacizumab and 2.9 days (2.6, 4.0) with placebo; there was a trend toward faster time to platelet count response with caplacizumab, but this did not reach significance (P = .05; HR 1.67 [95% CI: 1.03, 2.72]) (Table 2). In patients with previous acute iTTP episodes, time to platelet count response was faster with caplacizumab compared with placebo; median (95% CI) time to platelet count response was 2.7 days (1.8, 2.8) with caplacizumab and 2.9 days (2.5, 3.7) with placebo (P = .04; HR 1.64 [95% CI: 0.95, 2.82]). Fewer patients experienced the composite outcome of iTTP-related death, exacerbation of iTTP, or a major TE with caplacizumab than those in placebo in both the de novo episode subgroup (6/47 [12.8%] with caplacizumab vs 19/34 [55.9%] with placebo) and the subgroup who had experienced previous acute episodes (3/24 [12.5%] with caplacizumab vs 17/39 [43.6%] with placebo) (Table 2). There were no iTTP-related deaths with caplacizumab in either subgroup, while there were 2 and 1 iTTP-related deaths in patients receiving placebo in the de novo iTTP and previous acute iTTP episodes subgroups, respectively (Table 2).

Among patients who had de novo iTTP, 2 of the 47 (4.3%) patients receiving caplacizumab experienced an exacerbation compared with 15 of the 34 (44.1%) on placebo; 4 of the 47 (8.5%) patients receiving caplacizumab in this subgroup had a relapse while none had a relapse with placebo. None of the 48 patients with de novo iTTP who received caplacizumab experienced refractory TTP, compared with 1 (2.9%) patient in the placebo group (Table 2). Among patients with previous acute iTTP episodes, 1 of the 24 (4.2%) and 13 of the 39 (33.3%) patients experienced an exacerbation on caplacizumab and placebo, respectively. Two of the 24 patients (8.3%) who had experienced previous acute iTTP episodes and received caplacizumab experienced a relapse, while no patients on placebo had a relapse. None of the 24 patients who had experienced previous acute iTTP episodes and received caplacizumab experienced refractory TTP, compared with 2 (5.1%) patients on placebo. Recurrence (ie, exacerbation or relapse) mainly occurred in the form of relapse in patients who received caplacizumab and exacerbations in patients who received placebo (regardless of prior iTTP history in either case) (Table 2).

Among those with de novo iTTP who experienced recurrence during the overall study period, median (Q1, Q3) time to recurrence was 20 (10, 61) days for the placebo group vs 63 (53, 66) days with caplacizumab (HR [95%] CI: 5.76 [2.21, 15.03]; $P < .0001$). For those with history of previous acute iTTP episodes, median (Q1, Q3) time to recurrence was 61 (17, 66) days with placebo and 67 (63, 74.5) days with caplacizumab (HR [95%] CI: 3.63 [1.02, 13.00]; P = .03) (Supplementary Table S2, Figure A). Median (Q1, Q3) ADAMTS13 levels at time of recurrence were 2.5 (2.5, 4.0)% and 18 (2.5, 27.0)% for patients on placebo or caplacizumab, respectively, with prior iTTP (P = .48), and 2.5 (1.0, 6.0)% with caplacizumab vs 2.8 (2.0, 4.0)% with placebo for the de novo iTTP subgroup (P = .36) . ADAMTS13 levels at the time of exacerbation or recurrence (in all clinically relevant subgroups) are presented in Table 3.

3.1.2 | iTTP severity at presentation

At presentation, 90/145 patients (62.1%) had less severe disease, of whom 42/90 (46.7%) received caplacizumab and 48/90 (53.3%) were on placebo (Table 1). In the very severe group at presentation (55/145 [37.9%]), 30/55 (54.5%) were treated with caplacizumab while 25/55 (45.5%) received placebo (Table 1). Demographic characteristics and follow-up duration were generally balanced between the 2 subgroups (Table 1); those with less severe disease at presentation had a median (Q1, Q3) age of 42.0 (33.0, 54.0) years and 70.0% were female, while those with very severe disease at presentation had a median (Q1, Q3) age of 48.0 (43.0, 61.0) years and 67.3% were female. Among patients with less severe disease at presentation, 47/90 (52.2%) had de novo iTTP and 43/90 (47.8%) had previous acute iTTP episodes. Among patients with very severe disease at presentation, 35/55 (63.6%) presented with de novo iTTP vs 20/55 (36.4%) with previous acute iTTP episodes (Table 1).

In patients with less severe disease at presentation, there was a faster time to platelet count response in those treated with caplacizumab than placebo; median (95% CI) time to platelet count response was 2.7 days (1.8, 2.8) with caplacizumab and 2.8 days (2.7, 3.6) with

TABLE 1 Baseline characteristics by clinically relevant subgroup.

Baseline characteristic	Prior iTTP history		Disease severity at presentation[a]		Initial immunosuppression regimen[b,c]	
	De novo (n = 82)	Previous acute episode (n = 63)	Less severe (n = 90)	Very severe (n = 55)	Corticosteroids only (n = 112)	Corticosteroids + rituximab (n = 24)
Age (y), median (IQR)	45.5 (37.0, 58.0)	43.0 (35.0, 55.0)	42.0 (33.0, 54.0)	48.0 (43.0, 61.0)	45.0 (37.0, 55.0)	43.0 (34.5, 51.5)
Female, *n* (%)	56 (68.3)	44 (69.8)	63 (70.0)	37 (67.3)	74 (66.1)	18 (75.0)
Time from first symptom to diagnosis (d), median (IQR)	4.0 (1.0, 7.0)	2.0 (1.0, 4.0)	2.0 (1.0, 6.0)	3.0 (1.0, 7.0)	2.0 (1.0, 6.0)	4.5 (2.0, 7.5)
Follow-up time (d), median (IQR)	28.0 (27.0, 28.0)	28.0 (27.0, 29.0)	28.0 (27.0, 28.0)	28.0 (27.0, 28.0)	28.0 (27.0, 28.0)	28.0 (28.0, 29.0)
Prior TTP episodes, *n* (%)						
Initial	82 (100)	0	47 (52.2)	35 (63.6)	67 (59.8)	13 (54.2)
Recurrent	0	63 (100)	43 (47.8)	20 (36.4)	45 (40.2)	11 (45.8)
ADAMTS13						
<10%	71 (87.7)	52 (83.9)	74 (84.1)	49 (89.1)	97 (86.6)	23 (95.8)
≥10%	10 (12.3)	10 (16.1)	14 (15.9)	6 (10.9)	15 (13.4)	1 (4.2)
Platelet counts ($\times 10^9$/L)						
Mean (SD)	28.8 (22.3)	44.4 (32.8)	37.2 (27.7)	32.9 (29.5)	35.6 (28.0)	31.6 (28.4)
Median (IQR)	22.0 (12.0, 42.5)	27.0 (19.0, 68.0)	25.0 (16.0, 52.0)	20.0 (11.0, 49.0)	24.5 (15.0, 50.0)	23.0 (11.0, 42.0)
LDH (U/L), *n*	75	57	77	55	103	23
Median (IQR)	436 (359, 801)	346 (269, 564)	382 (267, 520)	559 (373, 993)	426 (301, 634)	411 (267, 515)
>ULN, *n* (%)	67 (89.3)	48 (84.2)	64 (83.1)	51 (92.7)	92 (89.3)	19 (82.6)
Cardiac troponin I (μg/L), *n*	75	57	77	55	103	23
Median	0.12	0.04	0.04	4.86	0.08	0.1
Range	0.01-75.96	0.01-74.89	0.01-0.14	0.01-75.96	0.01-75.96	0.01-4.44
>ULN, *n* (%)	46 (61.3)	25 (43.9)	17 (22.1)	54 (98.2)	56 (54.4)	13 (56.5)
Serum creatinine (μmol/L), *n*	75	57	77	55	103	23
Median (IQR)	81 (63, 108)	77 (63, 91)	71 (60, 87)	89 (69, 127)	80 (62, 105)	79 (65, 98)
>ULN, n (%)	19 (25.3)	11 (19.3)	10 (13)	20 (36.4)	24 (23.3)	5 (21.7)

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; iTTP, immune-mediated thrombotic thrombocytopenic purpura; LDH, lactate dehydrogenase; TTP, thrombotic thrombocytopenic purpura; ULN, upper limit of normal.

[a]Very severe disease at presentation was defined as French severity score ≥3 (score assesses presence of cerebral involvement, LDH >10 × ULN, and age [≤40/>40 to ≤60/>60 y] [17]) or severe neurologic involvement (measured by Glasgow coma scale score ≤12 [severe] or 13-15 [nonsevere]; score assesses aspects of best eye response, verbal response, and motor response, with lower scores indicating worse function [18]), or cardiac involvement (cardiac troponin I >2.5 × ULN). Assessment as severe/very severe as per any one of these criteria was sufficient for inclusion in the very severe subgroup.

[b]Nine patients received another form of immunosuppressive therapy (n = 1 for each: frontline cyclophosphamide, intensified cyclophosphamide [given after day 4], hydroxychloroquine, immunoglogulin human normal, mycophenolate mofetil, prednisolone, prednisone, methylprednisolone, methylprednisolone sodium succinate).

[c]Initial immunosuppression regimen was defined as therapy that was started up to day 3 of the treatment period.

TABLE 2 Efficacy outcomes by clinically relevant subgroup (ITT population).

Efficacy outcome	De novo iTTP (*n* = 82)		Previous acute iTTP episodes (*n* = 63)		Less severe disease at presentation[a] (*n* = 90)		Very severe disease at presentation[a] (*n* = 55)		Corticosteroids only (*n* = 112)		Corticosteroids + rituximab (*n* = 24)	
	Placebo (*n* = 34)	Caplacizumab (*n* = 48)	Placebo (*n* = 39)	Caplacizumab (*n* = 24)	Placebo (*n* = 48)	Caplacizumab (*n* = 42)	Placebo (*n* = 25)	Caplacizumab (*n* = 30)	Placebo (*n* = 54)	Caplacizumab (*n* = 58)	Placebo (*n* = 16)	Caplacizumab (*n* = 8)
Time to platelet count response (d)												
Median (Q1, Q3)	2.9 (2.0, 5.7)	2.6 (1.7, 3.8)	2.9 (1.9, 3.9)	2.7 (1.8, 2.9)	2.8 (2.0, 3.8)	2.7 (1.7, 2.9)	3.5 (1.9, 5.7)	2.7 (1.7, 3.8)	2.9 (1.9, 4.0)	2.7 (1.7, 2.9)	2.8 (2.6, 3.9)	2.7 (2.0, 4.2)
95% CI[b]	(2.6, 4.0)	(1.8, 2.9)	(2.5, 3.7)	(1.8, 2.8)	(2.7, 3.6)	(1.8, 2.8)	(2.0, 5.7)	(1.8, 2.9)	(2.7, 3.8)	(1.9, 2.9)	(2.5, 3.7)	(1.6, 4.7)
P value[c]	.05		.04		.03		.11		.007		.89	
Time to platelet count response, normalization hazard ratio (95% CI)[d]	1.67 (1.03, 2.72)		1.64 (0.95, 2.82)		1.59 (1.02, 2.47)		1.69 (0.94, 3.04)		1.85 (1.23, 2.77)		0.92 (0.37, 2.29)	
Composite outcome,[e] *n* (%)[f]	19 (55.9)	6 (12.8)[g]	17 (43.6)	3 (12.5)	24 (50.0)	2 (4.9)[h]	12 (48.0)	7 (23.3)	26 (48.1)	7 (12.1)	9 (56.3)	1 (12.5)
TTP-related death, *n*[i](%)	2 (5.9)	0	1 (2.6)	0	1 (2.1)	0	2 (8.0)	0	2 (3.7)	0	0	0
Exacerbation of TTP, *n* (%)[f]	15 (44.1)	2 (4.3)[g]	13 (33.3)	1 (4.2)	20 (41.7)	0	8 (32.0)	3 (10.0)	20 (37.0)	3 (5.2)	8 (50.0)	0
Major TE event, *n* (%)[i]	3 (8.8)	4 (8.3)	3 (7.7)	2 (8.3)	3 (6.3)	2 (4.8)	3 (12.0)	4 (13.3)	5 (9.3)	4 (6.9)	1 (6.3)	1 (12.5)
Recurrence of TTP,[j] *n* (%)[f]	15 (44.1)	6 (12.8)[g]	13 (33.3)	3 (12.5)	20 (41.7)	5 (12.2)[h]	8 (32.0)	4 (13.3)	20 (37.0)	7 (12.1)	8 (50.0)	1 (12.5)
Relapse of TTP,[k] *n* (%)[f]	0	4 (8.5)[g]	0	2 (8.3)	0	5 (12.2)	0	1 (3.3)	0	4 (6.9)	0	1 (12.5)
Refractory TTP, *n* (%)[g]	1 (2.9)	0	2 (5.1)	0	1 (2.1)	0	2 (8.0)	0	1 (1.9)	0	1 (6.3)	0

ITT, intention-to-treat; iTTP, immune-mediated thrombotic thrombocytopenic purpura; TE, thromboembolic; TTP, thrombotic thrombocytopenic purpura.

[a]Very severe disease at presentation was defined as French severity score ≥3 (score assesses presence of cerebral involvement, lactate dehydrogenase > 10 × upper limit of normal [ULN], and age [≤40/>40 to ≤60/>60 y] [17]), or severe neurologic involvement (measured by Glasgow coma scale score ≤12 [severe] or 13-15 [nonsevere]; score assesses aspects of best eye response, verbal response and motor response, with lower scores indicating worse function [18]), or cardiac involvement (cardiac troponin I >2.5 × ULN). Assessment as severe/very severe as per any one of these criteria was sufficient for inclusion in the very severe subgroup.

[b]Derived using Kaplan-Meier method.

[c]Derived based on log-rank test.

[d]Cox proportional hazards model with treatment group and Glasgow coma scale category as independent variables. The placebo group was considered as the reference to compute the hazard ratio.

[e]Composite outcome of TTP-related death, recurrence of TTP (exacerbation), or major TE event during the blinded treatment period.

[f]Percentages were calculated based on assessed patients.

[g]47 subjects were assessable for this event.

[h]41 subjects were assessable for this event.

[i]Percentages were calculated based on *n* for each subgroup.

[j]Recurrence of TTP during the overall study period.

[k]Occurences of relapse before the treatment switch are considered.

placebo (P = .03; HR 1.59 [95% CI: 1.02, 2.47]). In patients with very severe disease at presentation, there was a trend toward faster time to platelet count response, but this did not reach significance; median (95% CI) time to platelet count response was 2.7 days (1.8, 2.9) with caplacizumab and 3.5 days (2.0, 5.7) with placebo (P = .11); HR 1.69 [95% CI: 0.94, 3.04]). Fewer patients experienced the composite outcome of iTTP-related death, exacerbation, or major TE with caplacizumab than placebo in both the less severe subgroup (2/41, 4.9% vs 24/48, 50.0%) and the very severe subgroup (7/30, 23.3% vs 12/25, 48.0%). There were no iTTP-related deaths with caplacizumab in either subgroup, while there were 1 and 2 iTTP-related deaths in patients receiving placebo in the less severe and very severe disease subgroups, respectively (Table 2).

No patients treated with caplacizumab developed refractory disease in either subgroup. In patients receiving placebo, 1 and 2 patients experienced refractoriness in the less severe and very severe disease at presentation subgroups, respectively. Among those treated with caplacizumab, no exacerbations occurred in the less severe group and 3/30 patients (10%) experienced an exacerbation in the very severe group. For those on placebo, 20 (41.7%) and 8 (32%) patients had an exacerbation in the less severe and very severe disease subgroups, respectively. In patients receiving caplacizumab, 5 patients (12.2%) in the less severe disease group and 1 patient (3.3%) in the very severe disease group experienced a relapse, while no patients on placebo had a relapse. Recurrence in patients who received caplacizumab was mainly driven by relapse in patients with less severe disease and by exacerbation in patients with very severe disease (Table 2).

Among patients with less severe disease at presentation who experienced recurrence, median (Q1, Q3) time to recurrence was 32 (11, 64) days for the placebo group vs 64 (61, 69) days for the caplacizumab group (HR [95%] CI: 5.23 [1.95, 14.07]; P = .0003). For those with very severe disease at presentation, median (Q1, Q3) time to recurrence was 37 (12, 64) days among the placebo group vs 63.5 (60, 71) days in the caplacizumab group (HR [95%] CI: 3.22 [0.96, 10.72]; P = .04) (Supplementary Table S2, Figure B). Median (Q1, Q3) ADAMTS13 levels at time of recurrence were 2.5% (1.5%, 3.5%) with placebo and 2.5% (2.5%, 3.0%) with caplacizumab for patients with less severe disease at presentation (P = .92) and 3.75% (2.5%, 7.0%) with placebo vs 6.15% (3.0%, 17.7%) with caplacizumab for those with very severe disease at presentation (P = .91).

3.1.3 | Initial immunosuppression regimen

A total of 112 of the 145 patients received corticosteroids only as their initial immunosuppressive therapy (77.2%), while 24 of the 145 patients (16.6%) received a combination of corticosteroids and early rituximab (initiated within the first 3 days of the study) (Table 1). Demographics, clinical characteristics, and follow-up duration between the 2 subgroups were well balanced (Table 1). Median (Q1, Q3) age was 45.0 (37.0, 55.0) years among patients receiving corticosteroids only (66.1% female) and 43.0 (34.5, 51.5) years among those receiving corticosteroids and rituximab (75.0% female).

Intensification of immunosuppressive therapy was required for 38 of the 112 patients (33.9%) who initially received corticosteroids only and 3 of the 24 (12.5%) patients who initially received corticosteroids and rituximab. The corticosteroid-only group included 19 patients in each treatment group; intensification was often through the addition of rituximab. Median time from treatment start to first intensification was 12 days (range, 4-75 days) for the placebo group vs 17 days (range, 4-90 days) for the caplacizumab group. Intensification occurred in the double-blind treatment period for the majority of the patients (13/19 and 14/19 patients in the placebo and caplacizumab groups, respectively), whereas for the rest intensification occurred within the open-label treatment or follow-up periods (3/19 and 3/19, respectively, for the placebo group; 0/19 and 5/19, respectively, for the caplacizumab group). There is limited information available on reasons for treatment intensification, but low ADAMTS13 levels were flagged in the majority of patients in both treatment groups (17/19 in each group) in the week prior to intensification. The 3 patients who received corticosteroids and rituximab as initial immunosuppressive therapy were all in the caplacizumab treatment group; these patients received mycophenolate mofetil (with or without bortezomib) as intensification therapy (Table 4). Median time to intensification for these 3 patients was 12 days (range, 5-41 days) and occurred in the double-blind treatment period for 2 of the 3 patients and during the follow-up period for the remaining patient. In the corticosteroid-only subgroup, 67 of the 112 patients (59.8%) presented with de novo ITP while 45 of the 112 (40.2%) had previous acute iTTP episodes. Among those receiving corticosteroids and rituximab, 13 of the 24 patients (54.2%) had de novo iTTP and 11 of the 24 (45.8%) had previous acute iTTP episodes (Supplementary Table S3).

In patients receiving corticosteroids only, median (95% CI) time to platelet count response was shorter for those receiving caplacizumab (2.7 days [1.9, 2.9]) than for those receiving placebo (2.9 days [2.7, 3.8]; P = .007; HR 1.85 [95% CI: 1.23, 2.77]). In patients receiving corticosteroids and rituximab, no differences were seen between treatment groups in median (95% CI) time to platelet count response; 2.7 (1.6, 4.7) days with caplacizumab and 2.8 (2.5, 3.7) days with placebo (P = .89; HR 0.92 [95% CI: 0.37, 2.29]) (Table 2). Among those receiving corticosteroids only, the median (95% CI) time to sustained ADAMTS13 activity of ≥20% from starting placebo was 22.0 (9.0, 54.0) days (n = 37/54) and 28.0 (13.0, 43.0) days from starting caplacizumab (n = 39/58). In the corticosteroid-only subgroup, 38.5% (20/52) on placebo and 30.9% (n = 17/55) receiving caplacizumab had sustained ADAMTS13 activity of ≥20% 7 days after stopping TPE. At 30 days after TPE, 51.9% (27/52) of patients receiving placebo in the corticosteroid-only subgroup did not have sustained ADAMTS13 of ≥20% compared with 50.9% (28/55) of patients receiving caplacizumab. Among those receiving corticosteroids in combination with rituximab, the median (95% CI) time to sustained ADAMTS13 activity of ≥20% was 39.0 (6.0, 62.0) days in the placebo group (n = 13/16) and 21.5 (6.0, 28.0) days in the caplacizumab group (n = 7/8). In the corticosteroid + rituximab subgroup, 18.8% (3/16) of those on placebo and 37.5% (3/8) of those receiving caplacizumab had sustained ADAMTS13 activity of ≥20%, 7 days after stopping TPE. At 30 days

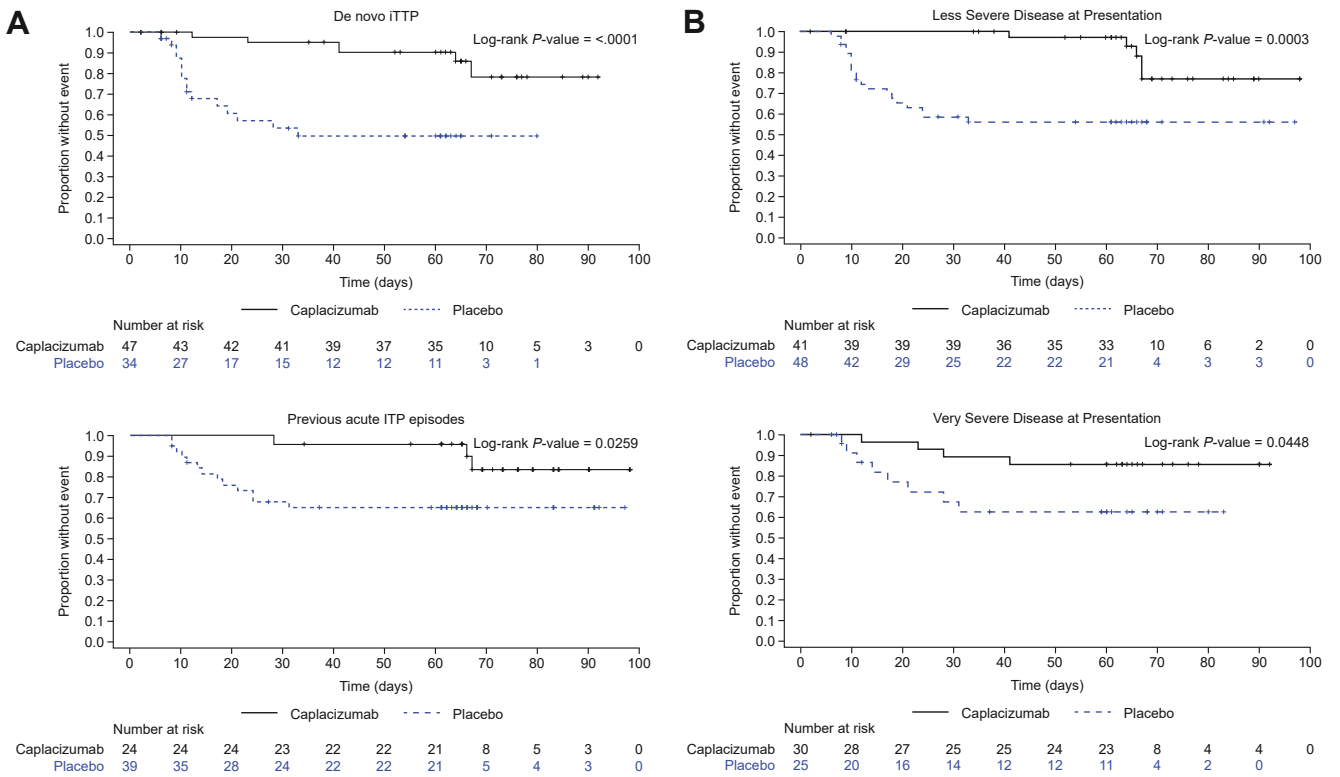


FIGURE Time to recurrence by (A) prior iTTP history and treatment group, (B) disease severity at presentation and treatment group, and (C) initial immunosuppression regimen and treatment group. iTTP, immune-mediated thrombotic thrombocytopenic purpura.

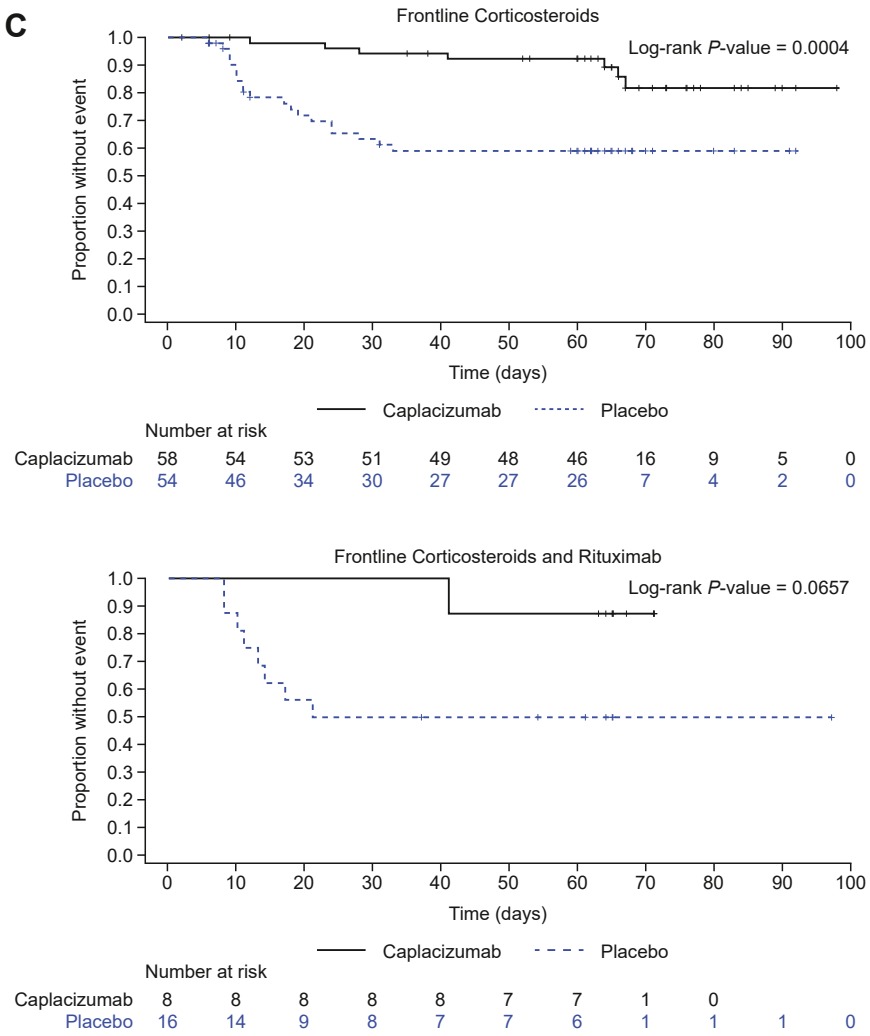
after TPE, 68.8% (11/16) of patients receiving placebo in the corticosteroid + rituximab subgroup did not have sustained ADAMTS13 of ≥20% compared with 12.5% (1/8) of patients receiving caplacizumab (Supplementary Table S4).

Fewer patients experienced the composite outcome of TTP-related death, exacerbation, and major TE with caplacizumab vs placebo in both subgroups (Table 2). In the corticosteroid-only subgroup, 7 of the 58 patients (12.1%) experienced the composite outcome in the caplacizumab group compared with 26 of the 54 (48.1%) in the placebo group, while in the corticosteroid plus rituximab subgroup, 1 of the 8 patients (12.5%) experienced the composite outcome with caplacizumab compared with 9 of the 16 patients (56.3%) with placebo.

In the placebo arm, 20 of the 54 patients (37.0%) and 8 of the 16 patients (50.0%) experienced an exacerbation in the corticosteroid-only subgroup and the corticosteroid plus rituximab subgroup, respectively. In the caplacizumab group, 3 of the 58 patients (5.2%) experienced an exacerbation in the corticosteroid-only group, while no patients receiving corticosteroids and rituximab experienced an exacerbation (Table 2). Two of the 3 caplacizumab-treated patients with exacerbations had received their last caplacizumab dose 0 days prior to exacerbation, while the third patient received the last dose 7 days prior to exacerbation. All 3 patients tested positive for antidrug antibodies (ADAs); 1 patient developed an ADA before experiencing exacerbation, while the other 2 patients developed an ADA at least once after exacerbation. In the placebo group, no patients experienced a relapse in either subgroup, while 4 of the 58 patients (6.9%) in the corticosteroid-only group and 1 of the 8 patients (12.5%) receiving corticosteroids and rituximab experienced a relapse in the caplacizumab group. No caplacizumab-treated patient developed refractory TTP in either the corticosteroid-only subgroup or the corticosteroid plus rituximab subgroup, whereas of those treated with placebo, 1 patient in each subgroup had refractory TTP. There were no TTP-related deaths with caplacizumab in either subgroup, while in the placebo group, 2 patients had a TTP-related death in the corticosteroid-only subgroup (Table 2). In patients receiving corticosteroids only, 7 of the 58 (12.1%) in the caplacizumab group experienced TTP recurrence (ie, 4 cases of relapse and 3 exacerbations) during the overall study period compared with 20 of the 54 (37.0%) in the placebo group (all exacerbations). In patients receiving corticosteroids and rituximab, 1 of the 8 patients (12.5%) in the caplacizumab group experienced recurrence (in the form of relapse) compared with 8 of the 16 (50.0%) in the placebo group (all exacerbations).

Among those receiving corticosteroids only as their initial immunosuppressive regimen, median (Q1, Q3) time to recurrence was 46 (11, 65) days in the placebo group vs 64 (60, 73) days in the caplacizumab group (HR [95%] CI: 4.20 [1.77, 9.97]; P = .0004). For those who received corticosteroids and rituximab as their initial immunosuppressive therapy, median (Q1, Q3) time to recurrence was 29 (12, 62.5) days among the placebo group vs 64.5 (63, 66) days in the caplacizumab group (HR [95%] CI: 6.15 [0.75, 50.71]; P = .07) (Supplementary Table S2, Figure C). Median (Q1, Q3) ADAMTS13 levels at time of recurrence were 2.5% (2.0%, 4.5%) and 3.0% (2.0%, 18.0%) for those on placebo or caplacizumab, respectively, receiving corticosteroids only (P = .66), and 2.5% (1.5%, 7.0%) with placebo vs

FIGURE Continued



4.0% (4.0%, 4.0%) with caplacizumab among patients on corticosteroids and rituximab (P = .77).

3.2 | Safety outcomes in clinically relevant subgroups

3.2.1 | iTTP history

The incidence of TEAEs was similar between caplacizumab and placebo, regardless of prior iTTP history. In the subgroup of patients with de novo iTTP, the proportion of patients experiencing at least 1 treatment-emergent SAE was lower with caplacizumab (18/47 [38.3%]) than with placebo (22/34 [64.7%]) (Table 5).

3.2.2 | Disease severity at presentation

The proportions of patients experiencing TEAEs were generally similar for caplacizumab and placebo, regardless of iTTP disease severity at presentation (Table 5). Fewer patients experienced treatment-emergent SAEs on caplacizumab compared with placebo in both disease severity subgroups. The most common bleeding-related adverse events in caplacizumab-treated patients across all disease severity subgroups were epistaxis (31.7%-33.3%) and gingival bleeding (16.7%-19.5%). Catheter site hemorrhage was reported in 5 caplacizumab-treated patients: 4 (13.3%) with very severe disease at presentation and 1 (2.4%) with less severe disease at presentation. In the placebo group, catheter site hemorrhage was reported in 2 (8.0%) and 3 (6.3%) patients, respectively.

3.2.3 | Initial immunosuppression regimen

Incidence of TEAEs was similar between caplacizumab and placebo, regardless of initial immunosuppression regimen. In each immunosuppressive therapy subgroup, the proportion of patients experiencing at least 1 treatment-emergent SAE was numerically lower with caplacizumab than that with placebo (Table 5). Among those receiving corticosteroids only, 21 of the 58 (36.2%) had at least 1 treatment-emergent SAE with caplacizumab compared with 28 of the 54 (51.9%) with placebo. Among patients receiving corticosteroids and rituximab, 2 of the 8

TABLE 3 ADAMTS13 levels at time of exacerbation and relapse by clinically relevant subgroup (ITT population).[a]

ADAMTS13 level	De novo iTTP (*n* = 82)		Previous acute iTTP episodes (*n* = 63)		Less severe disease (*n* = 90)[b]		Very severe disease (*n* = 55)[b]		Corticosteroids only (*n* = 112)		Corticosteroids + rituximab (*n* = 24)	
ADAMTS13 levels at time of exacerbation (%)												
n	15	2	13	1	20	0	8	3	20	3	8	0
Median	2.5	5.2	2.5	27	2.5		3.8	8.3	2.5	8.3	2.5	
Q1, Q3	1.0, 6.0	2.0, 8.3	2.5, 4.0	27.0, 27.0	1.5, 3.5		2.5, 7.0	2.0, 27.0	2.0, 4.5	2.0, 27.0	1.5, 7.0	
Minimum, maximum	1.0, 64.0	2.0, 8.3	1.0, 66.3	27.0, 27.0	1.0, 64.0		1.0, 66.3	2.0, 27.0	1.0, 64.0	2.0, 27.0	1.0, 66.3	
Mean difference (95% CI)	−2.3 (−27.0, 22.4)		19.1 (−20.9, 59.0)		NE		0.7 (−30.7, 32.1)		6.2 (−11.5, 23.8)		NE	
P[c]	.8465		.3189		NE		.9604		.4768		NE	
ADAMTS13 levels at time of relapse (%)												
n	0	4	0	2	0	5	0	1	0	4	0	1
Median		2.8		10.3		2.5		4		2.8		4
Q1, Q3		1.8, 3.5		2.5, 18.0		2.5, 3.0		4.0, 4.0		1.75, 10.5		4.0, 4.0
Minimum, maximum		1.0, 4.0		2.5, 18.0		1.0, 18.0		4.0, 4.0		1.0, 18.0		4.0, 4.0

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ITT, intention-to-treat; NE, not estimable.

[a]The ADAMTS13 value on the same day of first occurrence of recurrence/exacerbation/relapse is considered. If ADAMTS13 value was not available on the same day of first occurrence of recurrence/exacerbation/relapse, then the closest date either before or after the first occurrence was considered. If the closest day was the same before and after the occurrence of recurrence/exacerbation/relapse, then the ADAMTS13 value after the occurrence or recurrence/exacerbation/relapse was considered.

[b]Very severe disease at presentation was defined as French severity score ≥3 (score assesses presence of cerebral involvement, lactate dehydrogenase >10 × upper limit of normal [ULN] and age [≤40/>40 to ≤60/>60 y] [17]), or severe neurologic involvement (measured by Glasgow coma scale score ≤12 [severe] or 13-15 [nonsevere]; score assesses aspects of best eye response, verbal response, and motor response, with lower scores indicating worse function [18]), or cardiac involvement (cardiac troponin I >2.5 × ULN). Assessment as severe/very severe as per any one of these criteria was sufficient for inclusion in the very severe subgroup.

[c]*P* value was derived from 2-sample *t*-test.

TABLE 4 Additional therapies used for immunosuppressive therapy intensification in patients receiving corticosteroids with or without rituximab at baseline.

	Corticosteroids only (n = 112)		Corticosteroids + rituximab (n = 24)	
Additional therapy	Placebo (n = 54)	Caplacizumab (n = 58)	Placebo (n = 16)	Caplacizumab (n = 8)
Any intensification, n (%)[a,b]	19 (35.2)	19 (32.8)	0	3 (37.5)
Rituximab	19 (100.0)	18 (94.7)	0	0
Mycophenolate mofetil	0	1 (5.3)	0	3 (100)
Splenectomy	1 (5.3)	1 (5.3)	0	0
Bortezomib	0	1 (5.3)	0	1 (33.3)
Hydroxychloroquine	0	1 (5.3)	0	0
Plasma[c]	1 (5.3)	0	0	0

[a]Intensified immunosuppression was defined as start of immunosuppression therapy from day 4 or later.
[b]The denominator for percentages for "any intensification" is based on treatment totals in each subgroup. The denominator for percentages for additional medications are based on those with "any intensification."
[c]Based on investigator reporting.

(25%) in the caplacizumab group experienced at least 1 treatment-emergent SAE compared with 10 of the 16 (62.5%) in the placebo group. The addition of rituximab to the immunosuppression regimen did not appear to affect caplacizumab safety outcomes (Table 5).

4 | DISCUSSION

These post hoc analyses confirm the efficacy of caplacizumab in clinically diverse subpopulations of patients with iTTP, regardless of clinical features at presentation. Our findings demonstrate the early and sustained benefit of caplacizumab over placebo, irrespective of prior iTTP history, disease severity at presentation, or initial immunosuppression regimen.

Although the disease course in iTTP is often unpredictable, studies indicate that advanced age, elevated LDH and raised cardiac troponin levels, and cerebral involvement suggest a poor prognosis [3,17,19–21]. Thus, while patients with very severe disease are considered to be at risk for poor outcomes, our analysis shows that, even among patients classified as having less severe disease at presentation, more than 40% experienced exacerbation within 30 days of responding to TPE and immunosuppression. Furthermore, regardless of prior iTTP history at presentation, patients in the placebo group were at high risk of iTTP-related death, exacerbation, or major TE event. This aligns with a report from the Ohio State University registry, where patients with de novo and previous iTTP episodes had similar clinical response, exacerbation, refractoriness, and mortality rates [22]. In our analyses, we found that patients with very severe disease at presentation also tended to be older (mean age 48.0 years compared with a mean age of 42.0 years for those with less severe disease at presentation), and severe disease was overrepresented among those with de novo iTTP. Of note, a clear treatment benefit with caplacizumab was demonstrated in patients with iTTP irrespective of disease severity at presentation or whether they presented with de novo iTTP or previous acute iTTP episodes. This highlights the importance of starting caplacizumab therapy in all patients with iTTP. Of the patients with less severe disease who received caplacizumab, 12.2% experienced relapse; however it should be noted that the numbers were small and effect implausible as caplacizumab is not expected to affect ADAMTS13 activity [23].

Rituximab treatment during the acute phase of iTTP has been shown to reduce the risk of relapse and mortality [24,25]. However, our findings demonstrate that despite receiving immunosuppressive therapy including early rituximab, patients remained at risk of exacerbations and refractoriness, events which typically occur in the first 2 to 3 weeks of disease presentation and prior to rituximab effect [26]. In this study, fewer patients experienced the composite TTP outcome of iTTP-related death, exacerbation of iTTP, or a major TE with caplacizumab compared with placebo in the corticosteroid-only subgroup and the corticosteroid plus rituximab subgroup; this was mainly driven by the higher number of exacerbations/recurrences in the 2 placebo subgroups compared with the 2 caplacizumab subgroups. Onset of action of rituximab is slow [26], and although it is likely to have an effect on longer-term disease control, its impact on exacerbations is currently unclear. Caplacizumab and rituximab have complementary modes of action, with caplacizumab providing early benefit by halting ongoing microthrombosis and rituximab addressing the underlying autoimmune disease by potentially inhibiting anti-ADAMTS13 antibody production [14]. International Society on Thrombosis and Haemostasis (ISTH) guidelines recommend early start of caplacizumab and rituximab (ie, at the time when a diagnosis of iTTP is confirmed [27]).

In the HERCULES study, ADAMTS13 activity was persistently low among patients experiencing iTTP recurrence [11]. Recent real-world evidence data reported similar results for patients with recurrent disease [13] and support the combined use of rituximab with caplacizumab, and continuation of caplacizumab until improvement in ADAMTS13 levels is observed [13,14]. In our analyses, median time to sustained ADAMTS13 activity of ≥20% was shorter among caplacizumab-treated patients who received corticosteroids plus rituximab (21.5 days) compared with those on placebo (39.0 days) and

TABLE 5 Safety outcomes by clinically relevant subgroup (safety population).

Safety outcome	De novo iTTP (*n* = 81)		Previous acute iTTP episodes (*n* = 63)		Less severe disease at presentation[a] (*n* = 89)		Very severe disease presentation[a] (*n* = 55)		Corticosteroids only (*n* = 112)		Corticosteroids + rituximab (*n* = 24)	
	Placebo (*n* = 34)	Caplacizumab (*n* = 47)	Placebo (*n* = 39)	Caplacizumab (*n* = 24)	Placebo (*n* = 48)	Caplacizumab (*n* = 41)	Placebo (*n* = 25)	Caplacizumab (*n* = 30)	Placebo (*n* = 54)	Caplacizumab (*n* = 58)	Placebo (*n* = 16)	Caplacizumab (*n* = 8)
≥1 TEAE, *n* (%)	33 (97.1)	46 (97.9)	38 (97.4)	23 (95.8)	46 (95.8)	39 (95.1)	25 (100)	30 (100)	52 (96.3)	56 (96.6)	16 (100)	8 (100)
≥1 treatment-emergent SAE, *n* (%)	22 (64.7)	18 (38.3)	17 (43.6)	10 (41.7)	25 (52.1)	15 (36.6)	14 (56.0)	13 (43.3)	28 (51.9)	21 (36.2)	10 (62.5)	2 (25.0)

iTTP, immune-mediated thrombotic thrombocytopenic purpura; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a]Very severe disease at presentation was defined as French severity score ≥3 (score assesses presence of cerebral involvement, lactate dehydrogenase >10 × upper limit of normal [ULN], and age [≤40/>40 to ≤60/>60 y] [17]), or severe neurologic involvement (measured by Glasgow coma scale score ≤12 [severe] or 13-15 [nonsevere]; score assesses aspects of best eye response, verbal response, and motor response, with lower scores indicating worse function [18]), or cardiac involvement (cardiac troponin I >2.5 × ULN). Assessment as severe/very severe as per any one of these criteria was sufficient for inclusion in the very severe subgroup.

compared with those who received caplacizumab and corticosteroids alone (28.0 days). Interestingly, patients on placebo who received both corticosteroids and rituximab took longer to normalize ADAMTS13 than those receiving corticosteroids only, although this was not significant; this may be due to small patient numbers. It should be noted that there are conflicting reports in the scientific literature concerning the impact of caplacizumab on time to ADAMTS13 recovery. Data from the Spanish Registry (*n* = 113 iTTP episodes) show that time to achieving ADAMTS13 activity of ≥20% was similar between caplacizumab-treated and non–caplacizumab-treated iTTP patients, but patients who were treated with caplacizumab early (ie, ≤3 days of iTTP diagnosis) took longer to achieve this target compared with patients who were treated with caplacizumab later (ie, >3 days after iTTP diagnosis) or non–caplacizumab-treated patients (early caplacizumab: median 20 days post-TPE; late caplacizumab: median 11 days post-TPE; noncaplacizumab treatment: median 13 days post-TPE). The authors noted that patients treated with early caplacizumab had a shorter duration of TPE than patients treated with late caplacizumab [28]. Conversely, a comparison of patients with iTTP treated with caplacizumab, immunosuppression, and TPE (*n* = 59 acute episodes) vs patients with iTTP treated with caplacizumab and immunosuppression only (*n* = 42 acute episodes) found that median time to recovery of ADAMTS13 activity of ≥20% after treatment initiation was longer for patients who received TPE compared with those who did not (37 vs 25 days) [29]. Finally, a recent analysis focusing on time to ADAMTS13 activity of >30% in patients with iTTP found that patients receiving caplacizumab (initiated within 48 hours of admission) took longer to achieve this target vs patients who did not receive caplacizumab (median 31 days vs 11.5 days post-TPE). The reasons for this are not clear, although authors noted that caplacizumab-treated patients required more doses of rituximab compared with non–caplacizumab-treated patients [30].

Safety outcomes among study population subgroups were consistent with the findings in the HERCULES study [11], with mucocutaneous bleeding events more frequently observed with caplacizumab. The impact of ADA in the HERCULES trial has been assessed in a separate analysis, with no impact observed on either efficacy or safety (poster presented at ISTH 2023 [31]). Regarding study limitations, it should be noted that race/ethnicity information was not available for the clinically relevant subgroups defined in this sstudy, which may limit the interpretation of these results. For context, 97 patients (67%) in the HERCULES trial were White, 28 patients were Black (19%), and 4 patients were Asian (3%); the remainder either described their race as "Other" or had missing data. A total of 6 patients (4%) were of Hispanic or Latino ethnicity [11]. Other limitations include the post hoc nature of the analyses, the lack of statistical testing, and heterogeneity in immunosuppressive treatment regimens. Nonetheless, efficacy outcomes in each subgroup were consistent with findings from the main HERCULES study, which showed that caplacizumab reduced the time to platelet count normalization and decreased the incidence of TTP-related death, recurrence of TTP, or major TE event [11].

5 | CONCLUSIONS

In conclusion, this study adds to previous evidence for the efficacy and safety of caplacizumab in iTTP and reinforces the need for its use in clinically diverse subgroups. In this cohort, caplacizumab treatment in combination with TPE and immunosuppression improved the composite iTTP outcome of iTTP-related death, exacerbation, or major TE event in patients with iTTP, irrespective of de novo or previous acute prior iTTP history, initial immunosuppression regimen or disease severity at presentation. Regardless of initial immunosuppression regimen, risk of exacerbation was lower among patients receiving caplacizumab compared with placebo.

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AUTHOR CONTRIBUTIONS

M.S., P.C., J.A.K.H., F.P., S.C., J.d.l.R., and P.K. designed the study and collected, analyzed, and interpreted data. K.P. collected, analyzed, and interpreted data. S.G. and U.K. designed the study and analyzed and interpreted data. A.P.M. analyzed and interpreted data. All authors provided critical revision of the manuscript and had final approval of the manuscript for publication.

RELATIONSHIP DISCLOSURE

KP participated in studies of Ablynx/Sanofi, Bioverativ/Sanofi, Alexion, Roche, and Shire/Takeda and has received honoraria for speaking and consulting from Ablynx/Sanofi, Bioverativ/Sanofi, Shire/Takeda, Alexion, and Pfizer. MS has provided consultancy at advisory boards and received speaker fees from Ablynx/Sanofi, Shire/Takeda, and Novartis and research funding from Shire. PC is a member of advisory boards for and received speaker fees from Ablynx/Sanofi, Alexion, Takeda, and Janssen. SC has provided consultancy for and received research funding from Ablynx/Sanofi and Alexion. 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. 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. JdlR has provided consultancy at Ablynx/Sanofi, Amgen, Celgene, Janssen, and Pfizer and expert testimony at Amgen, Celgene, Janssen, and Pfizer. UK, APM, and SG are employees of Sanofi and may hold shares and/or stock options in the company.

DATA AVAILABILITY

Qualified researchers may request access to patient-level data and related study documents, which may include the 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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SUPPLEMENTARY MATERIAL

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