CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

CAPLACIZUMAB (CABLIVI)

(Sanofi Genzyme, a division of Sanofi-Aventis Canada Inc.)

Indication: Indicated for the treatment of adults with acquired thrombotic thrombocytopenic purpura (aTTP) in combination with plasma exchange (PEX) and immunosuppressive therapy

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Abbreviations

ADAMTS13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
AE	adverse event
aTTP	acquired thrombotic thrombocytopenic purpura
CDEC	CADTH Canadian Drug Expert Committee
CI	confidence interval
cTnI	cardiac troponin I
GCS	Glasgow Coma Scale
ICU	intensive care unit
ITT	intention-to-treat
LDH	lactate dehydrogenase
MAHA	microangiopathic hemolytic anemia
MCID	minimal clinically important difference
mITT	modified intention-to-treat
PEX	plasma exchange
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SE	standard error
SMMSE	Standardized Mini-Mental State Examination
TEAE	treatment-emergent adverse event
TTP	thrombotic thrombocytopenic purpura
ULN	upper limit of normal
vWF	von Willebrand factor
WDAE	withdrawal due to adverse event

Drug	Caplacizumab (Cablivi)
Indication	Indicated for the treatment of adults with acquired thrombotic thrombocytopenic purpura (aTTP) in combination with plasma exchange (PEX) and immunosuppressive therapy
Reimbursement request	As per indication
Dosage form(s)	Powder for solution (11 mg)
NOC date	February 28, 2020
Sponsor	Sanofi Genzyme, a division of Sanofi-Aventis Canada Inc.

Executive Summary

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare but serious thrombotic microangiopathy.[1] It is characterized by small-vessel platelet-rich thrombi that cause thrombocytopenia, microangiopathic hemolytic anemia (MAHA) and, sometimes, organ ischemia.[1,2] Acquired TTP (aTTP), which is due to autoantibodies against a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) and is usually associated with an ADAMTS13 activity level of less than 10%, is the most common form of TTP (95%). The incidence of aTTP was reported in the literature to be 1.2 to 13 cases per million. In Canada, the number of patients with aTTP was estimated to be 173 in 2018.[3] Since the development of therapeutic plasma exchange (PEX) or plasma infusion in the 1980s, mortality due to aTTP has decreased from 90% to a range of 10% to 20%.[1,4] Early diagnosis and treatment of aTTP is essential to the patient's survival. Despite advances in understanding the disease and evolving treatment regimens, surviving patients with aTTP are still at risk for TTP exacerbation or relapse, refractory disease, or long-term consequences such as cognitive deficits, depression, hypertension, renal impairment, development of systemic lupus erythematosus, and reduced life expectancy.[5-7]

Daily PEX plus immunosuppressive therapies (primarily corticosteroids) are the mainstay of treatment. It allows removal of anti-ADAMTS13 antibodies and replenishment of functional ADAMTS13 and von Willebrand factor (vWF). PEX has substantially reduced mortality rates and enables faster remission in patients with aTTP2,[8] although its use is associated with a number of adverse events (AEs). When there is a delay in delivering PEX, large-volume plasma infusions can be provided.[2] Rituximab is another immunosuppressive that is also recommended for patients with aTTP, especially for those with refractory or relapsing aTTP, in conjunction with PEX and steroids; however, rituximab does not have an indication for aTTP. Refractory patients can also be treated with cytotoxic drugs such as cyclophosphamide, and splenectomy.

Caplacizumab is a humanized, bivalent nanobody targeting the A1 domain of vWF to inhibit the interaction between vWF and platelets. On February 28, 2020, caplacizumab was approved by Health Canada for the treatment of adults with aTTP in combination with PEX and immunosuppressive therapy.[9] The recommended dose of caplacizumab is as follows:

- First day of treatment: 11 mg IV injection prior to PEX followed by an 11 mg subcutaneous injection after completion of PEX on that day.

- Subsequent days of treatment during PEX: daily 11 mg subcutaneous injection following PEX.
- Treatment after PEX period: 11 mg subcutaneous injections once daily for 30 days following the last daily PEX. If, after the initial treatment course, sign(s) of persistent underlying disease such as suppressed ADAMTS13 activity levels remain present, treatment may be extended for a maximum of 28 days.[9]

The CADTH Canadian Drug Expert Committee (CDEC) recommended that caplacizumab not be reimbursed for the treatment of adults with aTTP in combination with PEX and immunosuppressive therapy (March 6, 2020). A request for reconsideration was received by CADTH for this embargoed CDEC recommendation. The revised reimbursement criteria are for a narrower population: patients with multi-organ involvement indicating a more severe disease or refractory patients who do not respond well to previous treatment for a given time period, as determined by a specialist physician with expertise in treating aTTP.

Stakeholder Engagement

Patient Input

One patient group, the Answering TTP Foundation, submitted patient input for the review of caplacizumab for aTTP. Answering TTP is a volunteer-based organization that aims to provide patients with information about living with TTP by fostering research, providing support, and furthering education initiatives to improve the prognosis for patients living with TTP.

Answering TTP's submission was completed with assistance from the Canadian Organization for Rare Disorders. The two patient groups collaborated to develop the survey and interview questions to collect information from patients about aTTP and caplacizumab. The two groups also collaborated to conduct the interviews and summarize the feedback received. In total, 289 individuals provided feedback by completing the online survey or participating in interviews. Most of the respondents (83%) were patients with TTP.

The patient group describes the experience of living with this life-threatening disorder, saying that an aTTP episode has a significant impact on patients' and family members' quality of life. Patients also reported stress, altered mood, and the financial burden related to the disorder.

The outcomes patients expect from a new treatment are faster normalization of platelet counts, shorter hospital stays, quicker return to normal life, improved survival, and reduced aTTP episodes. Faster access to rapid care is also desired.

Clinician Input

Although PEX and immunosuppressants are effective, not all patients respond to these currently available treatments and, for some patients, the disease becomes refractory. In addition, the available treatment options are limited, especially for the patients with refractory disease. PEX is a temporary solution that removes the anti-ADAMTS13 antibodies; however, it is impossible to predict when these patients will have another aTTP episode. Gaining access to the treatments that may be effective is another challenge; some patients may have to go through a special access program to receive access to a specific treatment (e.g., rituximab) or obtain medications for off-label use.

There is a lack of standardization around the treatment protocols for aTTP across the specialized centres; for example, variabilities exist regarding access to PEX, when to start immunosuppression therapy such as rituximab and how aggressive the treatment should be, and how to taper PEX or steroids. This is associated with variable compliance among patients. There is also a gap in defining what qualifies a patient for more intensive treatment.

Although PEX is generally well tolerated, it can be time-intensive to set up (operationally) and requires specially trained personnel. PEX is typically available during the day. If patients arrive during off-hours, they will likely be treated with plasma infusion and/or IV immunoglobulin until the appropriate personnel are available. PEX also exposes patients to the risks associated with the transfusion of blood products.

The mechanism of caplacizumab is different from the current treatment paradigm. It targets the A1 domain of vWF and can be considered an anti-vWF drug that prevents the binding of vWF to the platelets. The panel indicated that from a resource and cost standpoint, caplacizumab probably wouldn't be used as first-line management or to replace the standard of care. Other standard-of-care drugs should be used continuously. Caplacizumab might be used for patients with multi-organ involvement indicating a more severe disease, or for refractory patients who do not respond well to previous treatment for a given time period. However, the panel noted that specifying criteria to identify these patients is difficult because of the current limited understanding of the disease and the variation in its natural history, caplacizumab's effect on natural history, and the lack of clinical data validating such an approach.

Adult patients best suited for treatment with caplacizumab might be those with very low platelet counts or multi-organ involvement in addition to the presentation of thrombocytopenia. They are considered to have more severe disease. However, there is a lack of agreed-upon criteria to quantify the severity of disease. Also, it is unknown if caplacizumab would provide more or less benefit for those with more severe forms of the disease. Patients should at least have a documented low ADAMTS13 level; however, this test is available only in specialized laboratories. Caplacizumab is contraindicated in patients who are hypersensitive to this drug. Caplacizumab should be used with caution in patients with impaired hepatic or renal functions, hemophilia, or coagulopathies. Patients with anti-drug antibody formation may not be suitable for this treatment.

In clinical practice, platelet counts are measured to determine whether a patient is responding to treatment for aTTP, with steadily increasing platelet counts and a count of higher than 150×10^9/L as one of the first metrics in terms of goals of care. Biochemistry laboratory results, such as lactate dehydrogenase (LDH), renal function (e.g., creatinine), hemoglobin, red blood cell fragments, and reticulocyte count are also measured. Clinically, if the patient is presenting with neurological abnormalities, improvements in the neurological symptoms are evaluated. ADAMTS13 activity and decreasing titres of ADAMTS13 inhibitors are useful measures of response to treatment. This specialized assay is now used in practice as well as in clinical studies. Patients are usually in hospital for at least five to seven days. During their hospitalization, their clinical response alongside the laboratory response are monitored daily. After the cessation of PEX, monitoring is still required to assess for relapse, although monitoring is not standardized in its frequency. In the clinical trials, patients were typically monitored for up to 30 days following the last treatment.

Discontinuation of caplacizumab should be considered in cases of worsening symptoms, or in cases where unacceptable AEs are present, such as increased bleeding (particularly in

the central nervous system and gastrointestinal tract), injection-site issues, autoantibody formation, or thrombosis, or any other AE that would be worth considering for discontinuation of treatment with caplacizumab.

It would be appropriate to have specialists or health care professionals with experience treating patients with TTP to diagnose, treat, and monitor patients who may receive caplacizumab. The clinical experts agreed that the drug would be initiated in the hospital and continued in an outpatient setting, which is appropriate once the patient's condition has clinically improved and there is no need to stay in the hospital after PEX is finished and when PEX can be done during an outpatient visit.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One phase III, double-blind, randomized controlled trial (RCT) (HERCULES, N = 145) submitted by the sponsor is included in this systematic review. The objective of HERCULES was to evaluate the efficacy and safety of caplacizumab in patients with aTTP. The trial included adult patients (≥ 18 years of age) with a clinical diagnosis of aTTP that presented with both thrombocytopenia and microscopic evidence of red blood cell fragmentation. Patients were excluded if they had platelet counts greater than 100×10^9/L at screening, had suspected thrombotic microangiopathies that were not associated with aTTP (such as hemolytic uremic syndrome), or if they had congenital TTP. Patients who had clinically significant active bleeding or a high risk of bleeding or were receiving chronic treatment with anticoagulant therapy that could not be stopped safely were also excluded. Eligible patients were randomized to receive caplacizumab 10 mg or placebo, in addition to standard of care, which consisted of PEX and corticosteroid treatment and other immunosuppressives. Note that even though the clinical trial protocol specified the caplacizumab dose as 10 mg, to be delivered by withdrawing all of the reconstituted solution from the vial and administering the full amount, a dose-recovery study showed that the mean dose that can be withdrawn from a vial is 11 mg, which is indicated in the product monograph for caplacizumab.[9] The double-blind treatment periods consisted of a daily PEX period and a 30-day post–daily PEX period. A treatment extension of seven to 28 days with caplacizumab or placebo was allowed for patients with risk factors for relapse of the presenting TTP episode. During the double-blind treatment period of HERCULES, in the case of first exacerbation or relapse of the presenting TTP episode, patients would receive open-label caplacizumab together with daily PEX irrespective of what the initial treatment allocation was. The primary efficacy outcome of this study was time to platelet count response, which was defined as an initial platelet count of 10×10^9/L or higher with the subsequent stopping of daily PEX within five days. Other efficacy outcomes include prevention of recurrence of aTTP, prevention of refractory aTTP, prevention of major thromboembolic events, normalization of organ damage markers, and length of intensive care unit (ICU) or hospital stays related to TTP episodes. Harm outcomes associated with the use of caplacizumab were also examined.

The major limitations of HERCULES include potential biases on the study results due to an imbalance in patients' baseline characteristics, uncertainty around the validity of using platelet count for treatment effect evaluation, substantial and disproportional missing data for some efficacy outcomes, and a lack of statistical testing for some of the secondary efficacy end points. Subgroup and sensitivity analyses were performed; however, the

results should be interpreted with caution, given the small sample size. Long-term clinical benefits and harms could not be explored in HERCULES due to the trial's short duration.

Efficacy Results

In HERCULES, the treatment effect of caplacizumab on survival, duration and volume of PEX, disease recurrence, refractory disease, organ damage, platelet response, neurological symptoms, cognitive change, and length of ICU and hospital stays related to aTTP episodes was examined.

Four TTP-related deaths were recorded during the overall study period; one patient from the caplacizumab group died during the drug-free follow-up period, and three patients from the placebo group died during the daily PEX period. One death from the placebo group was considered possibly related to the study drug, and all other deaths were considered not related to any of the treatments.

During the overall treatment period, treatment with caplacizumab was related to a shorter duration of PEX therapy compared with placebo (mean days on PEX: 5.8, standard error [SE] = 0.5 for caplacizumab versus 9.4 days, SE = 0.8 for placebo). Treatment with caplacizumab was also associated with reduced total PEX volume compared with placebo (21.3, SE = 1.6 litres versus 35.9, SE = 4.2 litres, respectively). According to the clinical experts consulted for this review, the between-group differences in the number of days on PEX and the PEX volume were considered clinically relevant.

During the overall study period, a statistically significantly lower percentage of patients in the caplacizumab group (nine patients, 12.7%) compared with the placebo group (28 patients, 38.4%) experienced recurrence of aTTP — either an exacerbation or a relapse. Exacerbations occurred in three patients (4.2%) treated with caplacizumab and 28 patients (38.4%) treated with placebo during the double-blind treatment period. During the follow-up period, relapses occurred in six patients (9.1%) treated with caplacizumab but in zero patients in the placebo group. The low recurrence of aTTP was attributed to the lower incidence of aTTP exacerbation in the caplacizumab group.

The median time to normalization of organ damage markers (e.g., LDH, cardiac troponin, serum creatinine) was 2.86 days (95% confidence interval [CI], 1.93 to 3.86) in the caplacizumab group and 3.36 days (95% CI, 1.88 to 7.71) in the placebo group, respectively. However, the between-group differences could not be considered statistically significant because the hierarchical statistical analysis plan failed to demonstrate statistical significance at a higher-order comparison.

During the overall treatment period, the number of patients experiencing major thromboembolic events was similar between the caplacizumab group (six patients, 8.5%) and the placebo group (six patients, 8.2%). The small number of events in the treatment groups makes it difficult to make conclusions.

During the double-blind treatment period, no patients in the caplacizumab group and three patients (4.2%) in the placebo group were considered to have refractory aTTP. The between-group difference in refractory aTTP was not statistically significant (P = 0.0572).

Time to platelet response was the primary efficacy end point in HERCULES. A statistically significantly shorter time to normalization of the platelet count was observed in the caplacizumab group (median = 2.69 days; 95% CI, 1.89 to 2.83) compared with the placebo group (median of 2.88 days; 95% CI, 2.68 to 3.56; P = 0.0099). A hazard ratio of 1.55 (95%

CI, 1.10 to 2.20) also suggested that at any given time point, patients in the caplacizumab group were 1.55 times more likely to achieve a platelet count response compared with those in the placebo group. However, the difference was not considered clinically relevant, according to the clinical experts consulted for this review.

There were numerical improvements in neurological symptoms and cognitive function from baseline, as well as shorter ICU days and hospitalizations during the overall study period with caplacizumab compared with placebo. However, HERCULES was not designed to assess the effects of caplacizumab on these outcomes, and limitations in the statistical analyses and missing data preclude drawing conclusions on these.

A phase II, single-blind RCT (TITAN) provided supportive evidence on treatment with caplacizumab. The efficacy of caplacizumab compared with placebo was demonstrated based on confirmed platelet response, which was the primary outcome in this study. Patients treated with caplacizumab were more likely to reach a confirmed platelet response compared with placebo based on a hazard ratio of 2.20 (95% CI, 1.28 to 3.78), which was statistically significant (P = 0.005).

Harms Results

During the overall study period, almost all patients reported AEs in HERCULES: 97.2% in the caplacizumab group and 97.3% in the placebo group. The majority of the AEs were of mild or moderate severity. The most common AEs reported in the caplacizumab group were epistaxis, headache, gingival bleeding, urticaria, pyrexia, fatigue, nausea, and TTP episodes. In the placebo group, TTP episodes, rash, and contusion were commonly reported. In the open-label caplacizumab therapy period, AEs were reported in 89.3% of patients. Catheter-site hemorrhage, epistaxis, gingival bleeding, and gastrointestinal symptoms were commonly reported.

SAEs were reported in 28 patients (39.4%) in the caplacizumab group and 39 patients (53.4%) in the placebo group during the overall study period. TTP episodes were the most commonly reported SAEs, and the incidence of TTP episodes was higher in the placebo group (39.7%) than in the caplacizumab group (12.7%). During the open-label caplacizumab therapy, seven patients (25%) reported SAEs.

[redacted]

Three patients in the placebo group died during the daily PEX treatment period. One patient in the caplacizumab group died in the follow-up period.

In terms of AEs of particular interest during the overall study period, the incidence of bleeding events was similar between treatment groups: 49 patients (69%) in the caplacizumab group and 49 patients (67.1%) in the placebo group. Hypersensitivity was experienced by 24 patients (33.8%) in the caplacizumab group and 22 patients (30.1%) in the placebo group. Anti-drug antibodies were found in two patients (2.8%) in the caplacizumab group and one patient (1.4%) in the placebo group.

[redacted]

Results from the TITAN study indicated that almost every patient experienced at least one AE, and more than half of them experienced at least one serious adverse event (SAE). The most common AEs and SAEs were TTP episodes. The most common AEs following TTP in the caplacizumab group were headache, epistaxis, and nausea, which was consistent with the results from HERCULES.

Table 1: Summary of Key Results From Pivotal and Protocol Selected Studies

	HERCULES	
	Caplacizumab (n = 72)	**Placebo (n = 73)**
Efficacy outcomes		
Death, n (%), overall study period	1 (1.9) occurred during follow-up period	3 (4.1) occurred during daily PEX period
Reduction in use of PEX, overall treatment period		
Duration of PEX, days, mean (SE)	5.8 (0.5)	9.4 (0.8)
Total volume of PEX, L, mean (SE)	21.3 (1.6)	35.9 (4.2)
Recurrence of aTTP, overall study period	9 (12.7)	28 (38.4)
Exacerbations, n (%)	3 (4.2)	28 (38.4)
Relapses, n (%)	6 (9.1)	0
Number of patients with ≥ 1 treatment-emergent major thromboembolic event, n (%), overall study period	6 (8.5)	6 (8.2)
Time to normalization of all 3 organ damage markers, days, median (95% CI), P value versus placebo[a]	2.86 (1.93 to 3.86)	3.36 (1.88 to 7.71)
Time to normalization of LDH, days, median (95% CI)	[redacted]	[redacted]
Time to normalization of cTnI, days, median (95% CI)	[redacted]	[redacted]
Time to normalization of creatinine, days, median (95% CI)	[redacted]	[redacted]
Number of patients with refractory aTTP, n (%), P value versus placebo,[b] DB study treatment period	0 P = 0.0572	3 (4.2)
Time to platelet count response, days, median (95% CI), P value versus placebo[a]	2.69 (1.89 to 2.83) P = 0.0099	2.88 (2.68 to 3.56)
Days in ICU related to aTTP, mean (SE)		
Daily PEX period	[redacted]	[redacted]
Overall treatment period, including open-label period	3.4 (0.40)	9.7 (2.12)
Overall treatment period, including follow-up period	[redacted]	[redacted]
Days in hospital related to aTTP, mean (SE)		
Daily PEX period	[redacted]	[redacted]
Overall treatment period, including open-label period	9.9 (0.70)	14.4 (1.22)
Overall treatment period, including follow-up period	[redacted]	[redacted]
Harm outcomes		
Patients with ≥ 1 AE, n (%)	69 (97.2)	71 (97.3)
Patients with ≥ 1 SAE, n (%)	28 (39.4)	39 (53.4)
Patients with ≥ 1 WDAE, n (%)	5 (7.0)	9 (12.3)
Notable harms, n (%)		
Bleeding event	49 (69.0)	49 (67.1)
Hypersensitivity	[redacted]	[redacted]

	HERCULES	
	Caplacizumab (n = 72)	Placebo (n = 73)
ADA positive	2 (2.8)	1 (1.4)

ADA = anti-drug antibody; AE = adverse event; aTTP = acquired thrombotic thrombocytopenic purpura; CI = confidence interval; cTnI = cardiac troponin I; DB = double-blind; LDH = lactate dehydrogenase; PEX = plasma exchange; SAE = serious adverse event; SE = standard error; TTP = thrombotic thrombocytopenic purpura; WDAE = withdrawal due to adverse event.

Note:

- Exacerbation: Defined as a recurrent thrombocytopenia after initial recovery of platelet count.
- Relapse: Defined as recurrent thrombocytopenia after initial recovery of platelet count requiring re-initiation of daily PEX and after discontinuation of caplacizumab.
- Refractory: Defined as the absence of platelet count doubling after four days of standard treatment and LDH > upper limit of normal.
- Platelet count response: Defined as initial platelet count ≥ 150 × 10^9/L with the subsequent stopping of daily PEX within five days of treatment.

[a] Calculated using stratified log-rank test.

[b] Cochran-Mantel-Haenszel test comparing caplacizumab group with placebo, adjusted for Glasgow Coma Scale at randomization.

Source: Clinical Study Report for HERCULES.[10]

Critical Appraisal

In HERCULES, appropriate methods were used to randomize patients to treatments and conceal treatment allocation. In general, patient characteristics appear to be balanced at baseline between groups, although some imbalance of these characteristics was also observed. Compared with the placebo group, patients in the caplacizumab group had fewer previous TTP episodes, more severe conditions, higher cardiac troponin I (cTnI) levels, and higher LDH levels at baseline. This imbalance in baseline characteristics may have an impact on data interpretation and could bias the results.

The treatment effects of the study drug were assessed at various periods, such as the double-blind daily PEX therapy period, the 30-day post–daily PEX period, the extension treatment period, and the open-label caplacizumab therapy period. Some patients who were initially assigned to the placebo group had to switch to caplacizumab therapy due to disease recurrence. This would complicate the data analysis and interpretation of the results for some of the efficacy outcomes, especially longer-term outcomes, for example, the risk of recurrence of aTTP in the future or days on PEX. In the analysis of the composite end point comprising TTP-related death, recurrence of aTTP, and occurrence of major thromboembolic events, switching to open-label caplacizumab therapy was not an issue for data analysis, as only events that had occurred prior to a switch to open-label caplacizumab were evaluated. For time to platelet count response, the primary efficacy outcome in HERCULES, the switch to open-label caplacizumab for those patients who experienced a recurrence of aTTP during the study did not affect the primary efficacy analysis, as a recurrence can occur only after platelet count response, according to the definition for this outcome (i.e., initial platelet count ≥ 150 × 10^9/L with the subsequent stopping of daily PEX within five days).

A hierarchical testing procedure was used to account for multiple comparisons among the primary end point and key secondary end points. The hierarchical sequence in the included studies was pre-specified and included clinically outcomes that were commonly accepted in thrombocytopenic disorders. Outcomes outside of the testing hierarchy, such as neurological assessment, cognitive assessments, and length of ICU or hospital stays need to be interpreted with caution due to the possible inflated type I error. In HERCULES, efficacy outcomes, except for the primary and key secondary outcomes, were descriptively summarized using the number of observations, means, and SEs. Formal statistical tests were not performed for these outcomes.

The study indicated that efficacy analyses were performed on an intention-to treat (ITT) population. However, a violation of ITT principles was observed in the analyses of several efficacy outcomes. [redacted]. In addition, the proportion of missing data was substantial (> 20%), as was the differential between caplacizumab and placebo for some of the efficacy outcomes, such as time to normalization of organ damage markers and cognitive assessments. Therefore, bias may have been introduced into the results. For the outcomes of platelet count response or days on PEX therapy, the impact of missing data would be minimal on the study results because all patients tended to complete the treatment with PEX. Missing data were not imputed for most of the outcome measures and no documented procedure was used to account for missing data, except for refractory aTTP, where a multiple imputation approach was adopted. The Clinical Study Report for HERCULES stated that all efficacy analyses were conducted on the ITT population; however, according to the data provided, many of the results were assessed using a subset of the randomized sample, so it seems that a modified ITT (mITT) population was used. Note that the ITT population included 145 patients, while the mITT population included 144 patients.

According to the clinical experts involved in the review, the inclusion and exclusion criteria for the study were reasonable and the included patient population was generally consistent with clinical practice. Misdiagnosis is common for aTTP, as other conditions may mimic aTTP. Although severe ADAMTS13 deficiency (activity < 10%) typically confirms a diagnosis of aTTP, activity less than 10% is not 100% sensitive or specific for aTTP, and aTTP patients who have received multiple PEX containing functional ADAMTS13 may have ADAMTS13 activity of 10% to 20%. In HERCULES, 10% to 18% of study participants had ADAMTS13 activity levels of 10% or higher. All patients received one PEX before randomization; this may have increased their ADAMTS13 levels at baseline. Four patients (5.6%) in the caplacizumab group and three patients (4.1%) in the placebo group who were initially diagnosed with aTTP had an alternative diagnosis later in the trial.[11] The misdiagnosis rate was low and is less likely to have had a significant impact on the generalizability of the study results. Due to the relatively short duration (two to six months) of the included study, some important clinical outcomes could not be sufficiently examined, such as survival, TTP relapses, and safety in the long run.

Other Relevant Evidence

Description of Studies

The TITAN study was included to supplement the review of caplacizumab in terms of providing additional safety and efficacy data. The TITAN study was a phase II, multi-centre, single-blind, parallel design, placebo-controlled RCT conducted in adult patients who were symptomatic and experiencing acute episodes of aTTP that required treatment with PEX. A total of 75 patients were included in the TITAN study: 36 received caplacizumab and 39 received placebo.

Efficacy Results

The efficacy of caplacizumab compared with placebo was demonstrated based on confirmed platelet response, which was the primary outcome in the TITAN study. Patients treated with caplacizumab were more likely to reach a confirmed platelet response compared with placebo, based on a hazard ratio of 2.20 (95% CI, 1.28 to 3.78), which was statistically significant (P = 0.005).

Harms Results

In terms of safety, almost every patient experienced at least one AE, and more than half of all patients experienced at least one SAE. The most common AE and SAE was TTP. The most common AEs following TTP (37% to 38% in both groups) in the caplacizumab and placebo groups, respectively, were headache (34.3% and 27.0%), epistaxis (31.3% and 10.8%), and nausea (28.6% and 29.7%). Of note, reports of serious TTP and bleeding events were more common among patients treated with caplacizumab compared with placebo, with TTP reported by [redacted] of patients treated with caplacizumab and placebo, respectively, and bleeding events reported by 54.3% and 37.8% of patients.

Critical Appraisal

Overall, the TITAN study demonstrated efficacy and highlighted safety signals that should be considered with the use of caplacizumab; however, the interpretation of the outcome data are limited due to concerns with the study's internal validity (more specifically, in terms of the single-blind study design, the potentially misleading choice of primary efficacy outcome, and the lack of adjustment for multiplicity and statistical testing), as well as its external validity in terms of generalizability to the Canadian context.

Conclusions

One phase III, double-blind, placebo-controlled, randomized trial provided evidence on the efficacy and safety of caplacizumab in adult patients with aTTP. Patients who received caplacizumab in addition to standard therapy (PEX and immunosuppressants) showed benefits in reducing the duration and volume for PEX, and reducing the frequency of aTTP exacerbations when comparing to placebo. There were no data on the impact of caplacizumab on subsequent aTTP recurrence beyond the trial observation period. Although only one of the four deaths in the trial occurred in the caplacizumab group and was considered by the blinded assessors as unrelated to treatment, the study was not designed to specifically assess survival. Therefore, it remains uncertain what the impact of caplacizumab is on survival and requires additional research. Caplacizumab improved platelet counts but it is unclear what the clinical relevance of this finding is. Almost all study participants reported treatment-emergent adverse events (TEAEs). A higher frequency of bleeding events occurred in the caplacizumab group, while patients who received placebo reported more TTP episodes. Most of the reported AEs were mild to moderate in intensity. A phase II single-blind RCT provided evidence to support the effect of caplacizumab on platelet response. The safety results in this trial were consistent with those in the phase III trial.

Conclusions regarding the long-term efficacy and safety of caplacizumab in patients with aTTP are lacking due to the short duration of treatment; in addition, the long-term results could be complicated by the use of open-label caplacizumab in some patients.

Introduction

Disease Background

TTP is a rare and serious thrombotic microangiopathy caused by reduced enzymatic activity of the vWF-cleaving protease, ADAMTS13.[1] Low activity of ADAMTS13 leads to large vWF multimers that can form platelet-rich thrombi in small blood vessels, typically located in the brain, heart, and kidneys. TTP manifests as thrombocytopenia, MAHA, and organ ischemia and is life-limiting.[1,2] It can be classified as aTTP, which is due to autoantibodies against ADAMTS13 and is usually associated with an ADAMTS13 activity level of less than 10%, and congenital TTP, which is due to ADAMTS13 gene mutations.[1] The most common form of TTP (95%) is aTTP, which can be induced by a certain drug or by infection, pancreatitis, surgery, pregnancy, or acute stress. The occurrence of congenital TTP is rare (5%).[2,3] The incidence of aTTP was reported to be 1.2 to 13 cases per million and mainly affects adults aged 30 to 50 years.[3] More women are affected (2:1 versus men).[3,5] In Canada, the number of patients with aTTP was estimated to be 173 in 2018.[3]

Without prompt appropriate treatment, the mortality rate can be as high as 90%, and half of the deaths occur within 24 hours of presentation.[2] Since the use of PEX or plasma infusion in the 1980s, mortality of aTTP has decreased to 10% to 20%.[1,4] Early diagnosis and treatment of aTTP is essential to the patient's survival. The diagnosis of aTTP is based on clinical and laboratory findings. When MAHA and thrombocytopenia present, aTTP should be considered.[1,2] Non-specific clinical manifestations such as fatigue, dyspnea, fever, myalgia, or arthralgia are common.[1] The platelet count is typically less than 30×10^9/L at presentation. Schistocytes (fragmented red blood cells) are found in a peripheral blood smear due to the mechanical damage caused when they pass through platelet-rich microthrombi in the small vessels. Other laboratory findings in patients with aTTP may include raised LDH values and troponin levels as markers of organ damage.[1,2,5] The activity of ADAMTS13 is reported as a percentage of normal plasma value, based on unaffected individuals. In general, severe deficiency (activity < 10% of normal) typically confirms the diagnosis of aTTP in the appropriate clinical setting (MAHA and thrombocytopenia without another obvious cause) and confirms the appropriateness of PEX and immunosuppressive therapy. Even though previous research reported that the diagnostic accuracy of ADAMTS13 activity testing for aTTP was high, with a sensitivity of 90% to 100% and specificity of 90% to 99%,[12,13] patients with sepsis or systemic cancer may have less than 10% ADAMTS13 activity, while aTTP patients who have received multiple transfusions of PEX containing functional ADAMTS13 may have ADAMTS13 activity of 10% to 20%.[1]

Despite the advances in understanding the disease and evolving treatment regimens, surviving patients with aTTP are still at risk for TTP exacerbation or relapse (affecting up to 84% of patients with aTTP, although the risk of relapse has been decreasing over time since the introduction of rituximab), refractory disease (approximately 10%), or long-term consequences such as cognitive deficits, depression, hypertension, renal impairment, development of systemic lupus erythematosus, and reduced life expectancy.[5-7]

Standards of Therapy

There are no published Canadian clinical practice guidelines for the management of aTTP.

Daily PEX (with spun apheresis, fresh frozen plasma, cryosupernatant, or plasma treated with solvent/detergent) plus immunosuppressive therapies (e.g., corticosteroids) are the

mainstay of treatment. PEX, which allows removal of the anti-ADAMTS13 antibodies and replenishment of functional ADAMTS13, has substantially reduced mortality rates and enables faster remission in patients with aTTP.[2,8] When a patient presents with MAHA and thrombocytopenia in the absence of any other identifiable clinical cause, clinical guidelines recommend that PEX be initiated as soon as possible, regardless of the time of day at presentation.[2] PEX should be given with 1 to 1.5 plasma volumes (calculated on the basis of sex, height, weight, and hematocrit) per treatment. The frequency and duration of the PEX procedure required to achieve remission is highly variable, depending on the disease and the patient's response to treatment. Daily PEX should continue for a minimum of two days and then stopped once the platelet count is greater than 150×10^9/L.[2,14] AEs during PEX therapy can be related to vascular access, replacement fluid, or the apheresis procedure itself; hypocalcemia (1.5% to 9%), hypovolemia (0.3% to 5%), or anaphylactoid reactions (0.7% to 12%) were reported. Rare AEs (approximately 1.5%), such as myocardial ischemia or infarction or shock, arrhythmia, respiratory arrest, pulmonary edema, pulmonary embolism, thrombosis or hemorrhage, infections, seizures, cerebrovascular ischemia, or hyperthermia, were also reported.[14] When there is a delay in delivering PEX, large-volume plasma infusions can be provided.[2]

British clinical practice guidelines recommend corticosteroids, either IV methylprednisolone or oral prednisolone, used in combination with PEX to manage allergic reactions during PEX. Corticosteroids are associated with minimal side effects.[2] Rituximab is another immunosuppressive that is recommended for patients with neurological or cardiac involvement, in conjunction with PEX and steroids. In addition, patients with refractory or relapsing aTTP should be offered rituximab.[2] Previous research has suggested that patients who received rituximab showed increased platelet levels, reduced anti-ADAMTS13 immunoglobulin G antibody levels, and increased ADAMTS13 activity, and the use of rituximab was related to decreased risk of aTTP relapse.[2,15,16]

In case of relapsing disease or disease exacerbation within the first month after stopping PEX, immediate readmission to hospital, re-initiation of PEX, and continuation of corticosteroids with rituximab are required.[7,16] For patients with refractory disease, the diagnosis should be re-evaluated to identify another cause of worsening symptoms or laboratory findings, such as sepsis related to the central venous catheter. Approaches for refractory disease may include: re-initiation of daily PEX if this has been discontinued (although there is no agreement on the benefit of using an intensified PEX regimen for such patients), an intensified glucocorticoid regimen, or initiation of rituximab therapy if the patient has not yet received rituximab for treatment of aTTP.[2,16] Refractory patients can also be treated with cytotoxic drugs, such as cyclophosphamide, and splenectomy. Splenectomy was used to treat TTP prior to the effective treatment with PEX. At present, splenectomy may be considered for patients with multiple relapses in preventing the frequency of subsequent relapses. However, this surgical procedure carries the risks of perioperative complications such as infections and thrombosis.[16]

Drug

Caplacizumab (Cablivi) is a humanized, bivalent nanobody targeting the A1 domain of vWF to inhibit the interaction between vWF and platelets. Therefore, it prevents ultra-large vWF-mediated platelet adhesion and subsequently prevents the formation of microthrombi. It also has an effect on the disposition of vWF and thus leads to transient reductions of total vWF antigen levels and to a concomitant reduction of factor VIII:C levels during treatment.[9] On February 28, 2020, caplacizumab was approved by Health Canada for the treatment of

adults with aTTP in combination with PEX and immunosuppressive therapy.[9] It is available as powder for solution, 11 mg per vial. The recommended dose of caplacizumab is as follows:

- First day of treatment: 11 mg IV injection prior to PEX followed by an 11 mg subcutaneous injection after completion of PEX on that day.
- Subsequent days of treatment during PEX: Daily 11 mg subcutaneous injection following PEX.
- Treatment after PEX period: 11 mg subcutaneous injection once daily for 30 days following the last daily PEX. If, after the initial treatment course, sign(s) of persistent underlying disease, such as suppressed ADAMTS13 activity levels, remain present, treatment may be extended for a maximum of 28 days.[9]

CDEC recommended that caplacizumab not be reimbursed for the treatment of adults with aTTP in combination with PEX and immunosuppressive therapy (March 6, 2020). A request for reconsideration was received by CADTH for this embargoed CDEC recommendation. The revised reimbursement criteria are for a narrower population: patients with multi-organ involvement indicating a more severe disease, or those with refractory disease that has not responded well to previous treatment for a given time period, as determined by a specialist physician with expertise in treating aTTP.

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

About the Patient Groups and Information Gathered

One patient group, the Answering TTP Foundation, submitted patient input for the review of caplacizumab for aTTP. Answering TTP is a volunteer-based organization located in Toronto with a board of directors composed of five members, two of whom are also patients. The Answering TTP Foundation aims to provide patients with information about living with TTP by fostering research, providing support, and furthering education initiatives to improve the prognosis for patients living with TTP (www.answeringttp.org).

Answering TTP's submission was completed with assistance from the Canadian Organization for Rare Disorders. More specifically, interviews and surveys were used to collect information from patients about aTTP and caplacizumab. The two patient groups collaborated to develop the survey and interview questions and Answering TTP identified interviewees and disseminated the survey through its website, Facebook, and email. The two groups also collaborated to conduct the interviews and summarize the feedback received.

Briefly, the online survey was available globally for approximately two weeks in July and August in 2019. In total, 289 individuals provided feedback by completing the online survey or participating in interviews. Most of the respondents (83%) were patients with TTP, 7% were a parent or guardian, 8% were a family member other than a parent, and the remainder were professional caregivers or patient advocates. The majority of survey respondents were diagnosed at or after the age of 20. Regarding the time since diagnosis, 28% had been diagnosed for more than 10 years, 21% for five to 10 years, 23% for two to five years, and 28% for less than two years. About 17% of the survey respondents were living in Canada, 63% were in the US, and the remaining were in Australia, the UK, and elsewhere. The interviews were conducted among patients (two from Ontario) and family members of patients (one from Alberta, one from the US).

Disease Experience

Patients were asked to rate symptoms commonly experienced during an episode of TTP using one of five options ranging from "no problem, never" and "minor, infrequent" to "serious, frequent" and "incapacitating, life-threatening." Approximately 61% reported fever, fatigue, headache, migraines, dizzy spells, and confusion as "serious, frequent," and 17% rated them as "incapacitating, life-threatening." About 53% of respondents reported bruises or red or purple spots on their skin as "serious, frequent" or worse; 21% rated them as "minor, infrequent" or less. Other symptoms reported included shortness of breath, chest pain, abdominal pain, kidney problems, and stroke and/or bleeding (from gums or nose), all of which were rated as "minor, infrequent" or less by the majority of patients (42% to 72%), with no more than 25% of patients rating them as "serious, frequent" or worse. Additionally, patients reported experiencing psychological and emotional effects, as well as confusion and/or memory loss, which was a "serious, frequent" or worse problem for 34% of respondents, and "no problem" or a "minor, infrequent" problem by 35% of patients.

The patient submission describes living with aTTP as unlike most chronic diseases because the challenges do not stem from the day-to-day experiences but, rather, are

mostly the result of acute TTP episodes that can be life-threatening and require intensive treatment. About half (49%) of respondents reported having had one to two relapses (episodes) since being diagnosed, and 21% had no relapses since remission. The remainder had three or more relapses since their last diagnosis. The time since last episode ranged from less than six months ago to more than 10 years ago. Further, 18% of respondents had been in remission for five to 10 years.

The submission also included comments provided by Canadian patients and families to reflect the experience with aTTP within the Canadian health care landscape. All the responses included in the submission highlighted the severity of an acute episode, with two of the three responses describing an episode that resulted in the patient dying. The input expressed a sense of frustration to physicians with expertise in diagnosing and managing the disease, and with receiving timely care for the acute episodes. The responses also describe a significant impact on quality of life as a result of an aTTP episode. Patients reported a financial burden due to an impact on their ability to work, lost income due to missed work, and the cost of paying for treatment. The financial burden, in addition to stress and altered mood, which were reported as side effects of treatments, also affect patients' friends and family. Respondents also described feelings of anxiety, worry, and fear about the onset of a future episode.

Experience With Treatment

Almost all respondents (99%) reported experience with plasmapheresis, and 96% with corticosteroids (85% in the past, 11% currently). Also, 70% had received or were currently receiving rituximab, and 13% had received or were receiving cyclosporine. Only 5% to 6% of the cohort had received caplacizumab. Splenectomy was also reported by 13% of the international cohort of respondents and by 22% of Canadian respondents.

The patient group input indicated that plasmapheresis works "well" or "very well" for 18% and 66% of patients, respectively, but there are challenges with timely access to administration. The limited options for effective treatments if plasmapheresis is unable to stabilize platelet counts were also noted as a real life-threatening challenge. Moreover, respondents highlighted variable levels of care and survival because guidelines or a protocol for treating an aTTP episode are limited. They also highlighted certain AEs with plasmapheresis. The 26 Canadian respondents who responded to a question about AEs with plasmapheresis reported experiencing hives (62%), chills or shivers (54%), fever (15%), and rash (15%) as well as urticaria and itching. More serious events included bleeding, infection, and anaphylactic shock. About 27% of the Canadian respondents reported anaphylactic reactions, both immediate and delayed, mild to severe, and lasting from a few weeks to several months.

AEs were also reported as an issue regarding treatment with corticosteroids. Most of the Canadian subset of survey respondents reported an increase in appetite and weight gain with corticosteroid use. Additionally, 77% reported mood changes, 58% reported fluid retention, 50% reported insomnia, and 35% reported muscle weakness. Osteoporosis (27%), bruising easily (23%), hypertension (19%), thinning of the skin (12%), diabetes (8%), eye disorders (8%), and infection (4%) were reported as well.

The submission noted that a combination of therapies during and after an episode is critical for patients; however, PEX and treatment with other drugs can be "onerous" due to the length of treatment, side effects, and lack of long-term effectiveness. Patients described extended lengths of time spend in hospital because they did not respond well to treatment, or related to removal of the spleen as a last resort after repeated treatment failure. Removal

of the spleen is also associated with complications, and therefore the need for a targeted TTP-fighting tool was expressed by patients. The following patient quote provides insight into the challenges associated with treatment:

> Plasmapheresis treatments are tough. It feels as if your whole body is humming… When I get a bag/a donor that I am more sensitive to, I might develop hives and get hot. As soon as I feel this, I would tell my nurse so she could give me another shot of Benadryl to counteract the reaction from the blood product. With every shot, I felt the rush of the Benadryl and I would try to give in and sleep. But mostly only my eyes close — the rest of my body is anxiously awake. I try not to think about the probability of a more serious reaction or side effect … Plasma exchange treatments save my life, but they also mean that my life is all of a sudden hijacked for extended hospital stays. This was easier when it just meant that I was off work and in hospital leaving my husband, parents, siblings and friends anxious about my recovery. This reaches a whole new level when you need to juggle kids and manage their emotions and real fears.

Twelve respondents (three from Canada) reported experience with caplacizumab through clinical trials or a special access program. The patient group submission summarized the feedback regarding treatment with caplacizumab as positive, particularly regarding time to response (platelet control recovery), time spent in hospital, and physical and mental well-being in terms of "energy and outlook." The patient quotes that were submitted noted the speed at which they responded to treatment and the ability to recover at home as an outpatient. Some felt more confident about looking to the future while receiving caplacizumab, while other reported uncertainty about how this will affect their risk of relapse. Patients also reported little to no side effects, and the AEs that were reported were "mild" and less significant. The following two quotes from patients were provided: "I think Cablivi would be great for most patients as long as they don't have a life-threatening risk of bleeding. For a first time diagnoses I think it would greatly help the patient return to normal life and would suffer less setbacks, memory loss or depression," and "Knowing that I will be guaranteed to have this again should I relapse is comforting."

Improved Outcomes

According to the patient submission, all respondents were provided with a summary of caplacizumab and how it would be used alongside plasmapheresis following an aTTP episode. The outcomes respondents expected from a new treatment were primarily faster normalization of platelet counts followed by shorter hospital stays, a quicker return to normal life, and improved survival. They also reported a desire for a reduced likelihood of another episode, acknowledging the challenges associated with measuring this. An additional theme throughout the response was the need for faster access to rapid care, as an episode needs to be treated immediately. One respondent noted that having a "booster" type of treatment could be useful in an emergent situation. In summary, patients want a treatment that will more safely and efficiently resolve an episode with fewer side effects over a shorter time period and prevent the occurrence of future episodes.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). In addition, as part of the caplacizumab review, a panel of four clinical experts from across Canada was convened to characterize unmet therapeutic needs, assist in identifying and communicating situations where there are gaps in the evidence that could be addressed through the collection of additional data, promote the early identification of potential implementation challenges, gain further insight into the clinical management of patients living with a condition, and explore the potential place in therapy of the drug (e.g., potential reimbursement conditions). A summary of this panel discussion is presented subsequently.

Description of the Current Treatment Paradigm for the Disease

The current treatment strategy for aTTP includes two components:

- PEX. PEX aims to replenish the ADAMTS13 metalloprotease and remove anti-ADAMTS13 antibodies, which are thought to be a part of the pathology of aTTP. Most patients receive PEX, which is given with 1 to 1.5 plasma volumes for five to seven days, to ensure the platelet count has improved and normalized before discontinuing the PEX. It was estimated that at least 70% of the patients respond to PEX. In general, PEX is well tolerated. The most common complications of PEX are allergic reactions (e.g., urticaria) and hypocalcemia, and the use of a catheter line also increases the risk of infection, bleeding, or thrombosis. The experts felt that anticipating these reactions by having medications such as antihistamines and other treatments makes them manageable in most cases. PEX therapy is available only in a few specialized hospital centres in Canada; therefore, access to PEX is restricted. When there is a delay in starting PEX, plasma infusion can be provided to replace the ADAMTS13 metalloprotease prior to initiating PEX. Plasma infusion can also be given to the patients who present to care without PEX, for example, those living in a rural area, as a stop-gap therapy while they wait to be transferred to receive PEX. Transfer to a centre with PEX typically occurs within one to two days.
- Immunosuppression with corticosteroids, with or without rituximab. Immunosuppressive therapy aims to reduce the production of ADAMTS13 autoantibodies. In recent years, rituximab has been studied for use both upfront and, more often, in treating refractory disease. Of note, rituximab does not have a Health Canada–approved indication for aTTP; therefore, it is being used off-label in the management of aTTP.

IV immunoglobulin, cyclophosphamide, or splenectomy may also be used for immune suppression, particularly for patients with refractory disease.

Caplacizumab targets the vWF-platelet interaction and prevents platelets from binding to vWF, thereby reducing the formation of microvascular thrombi and the subsequent organ ischemia.

Treatment Goals

The most important goals of an ideal treatment for aTTP are to prevent death, to prevent disability, to reduce multi-organ involvement of the disease, and to allow patients to return to a functional life.

Unmet Needs

Although PEX and immunosuppressants are effective, not all patients respond to these currently available treatments and, for some patients, the disease becomes refractory. In addition, the available treatment options are limited, especially for patients with refractory disease. At present, none of the available treatments can reverse the course of the disease. PEX is a temporary solution that removes the anti-ADAMTS13 antibodies; however, it is impossible to predict when the patients will have another aTTP episode.

There is a lack of standardization around the treatment protocols for aTTP across the specialized centres. For example, variability exists in access to the treatment, when to start the immunosuppression treatment, such as rituximab, and how aggressive the treatment should be, and how to taper PEX or steroids. This is associated with variable adherence among patients. Therefore, it becomes complicated when comparing one treatment algorithm from one centre with another treatment algorithm from another centre. There is also a gap in what qualifies a patient for more intensive treatment.

Although PEX is generally well tolerated, it can be time-intensive to set up (operationally) and requires specially trained personnel. PEX is typically available during the day. If patients arrive during off-hours, they will likely be treated with plasma infusion and/or IV immunoglobulin until the appropriate personnel are available. PEX also exposes patients to the risks associated with transfusion of blood products. Some literature suggests that more than 50% of the patients treated with PEX experienced a major AE, while the panel indicated that an AE rate of greater than 50% seems higher than their experience in clinical practice settings.

For patients with aTTP, a test of ADAMTS13 levels can be used for disease diagnosis and assessing treatment response. An increased ADAMTS13 level with treatment is preferred; however, an ADAMTS13 level will not be readily available in a timely manner in clinical practice compared with a platelet count.

Place in Therapy

The mechanism of caplacizumab is different from the current treatment paradigm: PEX and immunosuppression. Caplacizumab targets the A1 domain of vWF and can be considered an anti-vWF drug that prevents the binding of vWF to the platelets. It does not modify the underlying disease but treats a complication of aTTP.

The panel indicated that from a resource and cost standpoint, caplacizumab probably wouldn't be used as first-line management or to replace the standard of care. Other standard-of-care drugs should be used continuously. Caplacizumab might be used for patients with multi-organ involvement indicating a more severe disease, or for refractory patients who have not responded well to previous treatment for a given time period. However, the panel noted that specifying criteria to identify these patients is difficult because of the current limited understanding of the disease and the variation in its natural history, caplacizumab's effect on the disease's natural history, and the lack of clinical data validating such an approach.

Patient Population

Adult patients best suited for treatment with caplacizumab might be those with very low platelet counts or multi-organ involvement, such as neurological involvement or renal failure, in addition to the presentation of thrombocytopenia. They are considered to have more severe disease. However, there is a lack of agreed-upon criteria to quantify the

severity of disease. Patients should at least have a documented low ADAMTS13 level; however, this test is available only in specialized laboratories. The other approaches to quantifying the severity of disease, such as a specific number of organs involved or degree of organ involvement, have not been validated in clinical studies. Misdiagnosis is common, as other conditions (e.g., thrombocytopenia or red cell fragments on the blood smear from other causes) may mimic aTTP.

Caplacizumab is contraindicated in patients who are hypersensitive to this drug. Caplacizumab should be used with caution in patients with impaired hepatic or renal functions, hemophilia, or coagulopathies. Patients with anti-drug antibody formation may not be suitable for this treatment.

Assessing Response to Treatment

In clinical practice, platelet counts are measured to determine whether a patient is responding to treatment for aTTP, with steadily increasing platelet counts and a count greater than 150×10^9/L as one of the first metrics in terms of goals of care. In the absence of caplacizumab, the change in platelet counts would be a useful signal to assess response to treatment or worsening disease; however, because caplacizumab has a direct impact on the platelet counts but doesn't necessarily change the disease activity, it is more difficult to monitor how well a patient is responding and determine how to taper the existing therapy; thus, immunosuppressants should be optimized until the signs of underlying disease are resolved (e.g., sustained normalization of ADAMTS13 activity level).

Biochemistry laboratory results, such as LDH, renal function (e.g., creatinine), hemoglobin, red blood cell fragments, and reticulocyte count are also measured. Clinically, if the patient is presenting with neurological abnormalities, improvements in the neurological symptoms are evaluated. ADAMTS13 activity and decreasing titres of ADAMTS13 inhibitors are useful measures of response to treatment. This specialized assay is now used in practice as well as in clinical studies.

Patients usually stay in hospital for five to seven days or longer. During their hospitalization, their clinical response and laboratory response are monitored daily. After the cessation of PEX, monitoring is still required to assess for relapse, although this is not standardized in its frequency. In the clinical trials, patients were typically monitored for up to 30 days following the last treatment.

Discontinuing Treatment

Discontinuation of caplacizumab should be considered in cases of worsening symptoms or in cases where unacceptable AEs are present, such as increased bleeding (particularly in the central nervous system and gastrointestinal tract), injection-site issues, autoantibody formation, thrombosis, or any other AE that would be worth considering as a reason for discontinuation of treatment with caplacizumab.

Prescribing Conditions

It would be appropriate to have specialists or health care professionals with experience treating patients with TTP to diagnose, treat, and monitor patients who may receive caplacizumab. The clinical experts agreed the drug would be initiated in hospital and continued in an outpatient setting. This would be appropriate when the patient's condition has clinically improved and there is no need to stay in the hospital once PEX is finished, or when PEX can be done during an outpatient visit.

Clinical Evidence

The clinical evidence included in the review of caplacizumab is presented in two sections. Section 1, the systematic review, includes pivotal studies provided in the sponsor's submission to the CADTH Common Drug Review (CDR) and Health Canada, as well as those studies that were selected according to an a priori protocol. Section 2 includes additional relevant studies submitted by the sponsor that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of caplacizumab (powder and solvent for injection, 10 mg) for the treatment of aTTP in adult patients.

Methods

Studies selected for inclusion in the systematic review include pivotal studies provided in the sponsor's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 2.

Table 2: Inclusion Criteria for the Systematic Review

Patient population	Adults with aTTP Possible subgroups: • previous TTP episode (initial versus recurrent) • severity of disease • with or without previous rituximab
Intervention	Caplacizumab adjunct to PEX plus glucocorticoids ± immunosuppressants (e.g., rituximab) Caplacizumab administration: • First day: Caplacizumab 10 mg IV injection prior to PEX; caplacizumab 10 mg SC injection after completion of PEX • Subsequent days of treatment during PEX: Caplacizumab 10 mg SC injection q.d. following PEX • Subsequent days of treatment after PEX: Caplacizumab 10 mg SC injection q.d. for 30 days following the last daily PEX
Comparators	PEX plus glucocorticoids ± immunosuppressants (e.g., rituximab)
Outcomes	**Efficacy outcomes** • Survival • Reduction in use of PEX • aTTP relapse (e.g., time to relapse, proportion of patients with relapse)[a] • HRQoL[a] • Productivity (e.g., return to school or work, return to normal functioning)[a] • Organ damage markers (e.g., LDH, cardiac troponin, serum creatinine) • Prevention of major thromboembolic events (e.g., stroke, MI, pulmonary embolism, DVT) • Prevention of refractory aTTP to treatment • Response to treatment (e.g., time to response, proportion of responders)[a] • aTTP exacerbation[a] • Change in platelet counts from baseline • Neurological assessment • Cognitive assessment

	• Hospitalization due to aTTP episodes **Harms outcomes** • AEs, SAEs, WDAEs, mortality • Harms of special interest: Bleeding events, hypersensitivity, anti-drug antibodies (against caplacizumab) development
Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; aTTP = acquired thrombotic thrombocytopenic purpura; DVT = deep vein thrombosis; HRQoL= health-related quality of life; LDH = lactate dehydrogenase; MI = myocardial infarction; PEX = plasma exchange; q.d. = once daily; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the Peer Review of Electronic Search Strategies (PRESS) checklist (https://www.cadth.ca/resources/finding-evidence/press).[17]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid, Embase (1974–) through Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Cablivi (caplacizumab). Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on October 9, 2019. Regular alerts updated the search until the meeting of CDEC on February 19, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[18] Health Technology Assessment (HTA) Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 2 for more information on the grey literature search strategy.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

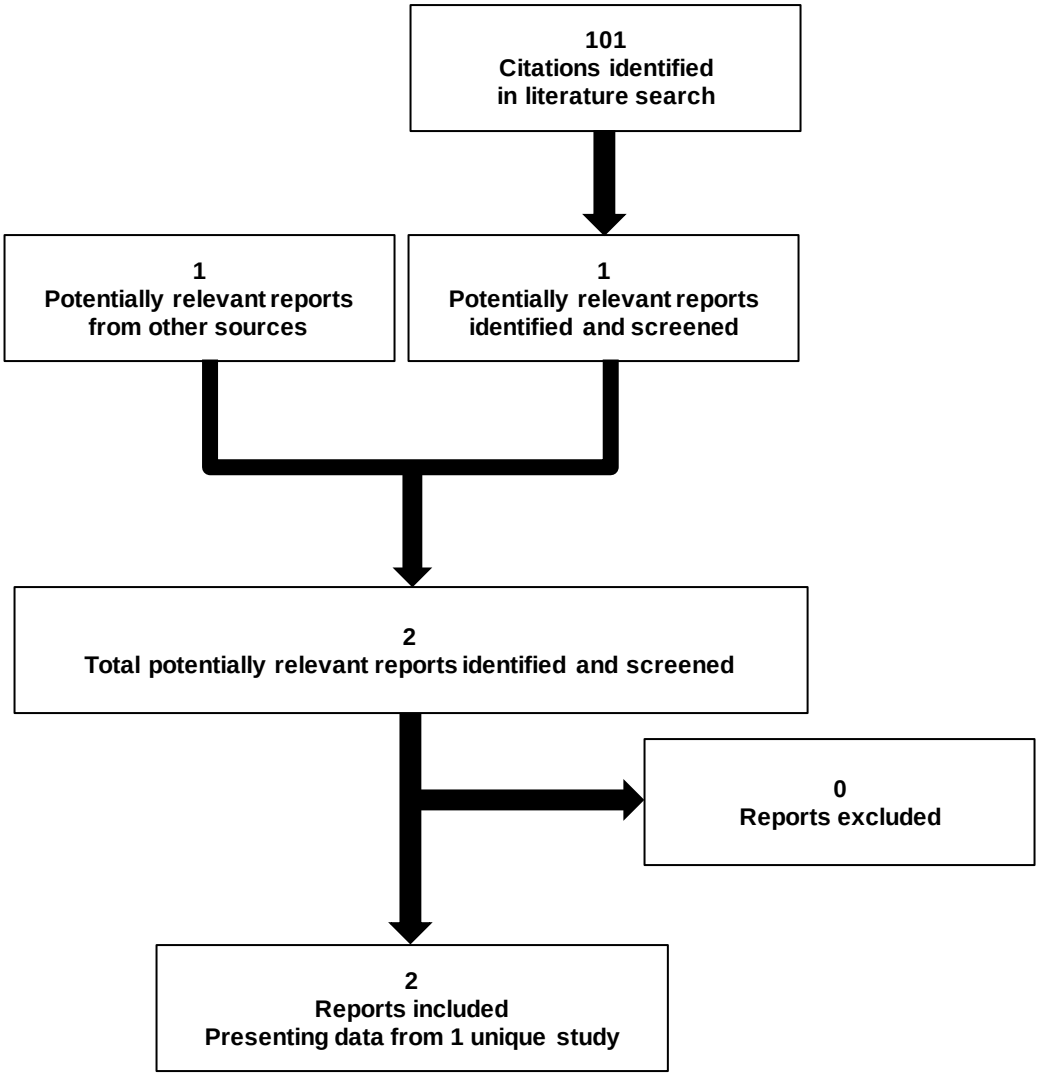


Table 3: Details of Included Studies

		HERCULES
Designs & Populations	**Study design**	Phase III, DB, placebo-controlled RCT
	Locations	55 centres in Canada, the US, Europe, and Australia
	Randomized (N)	145
	Inclusion criteria	• Adult patients ≥ 18 years of age • Clinical diagnosis of initial or recurrent aTTP • Negative pregnancy test for female patients of childbearing potential • Informed consent provided by patient or patient's representative
	Exclusion criteria	• Platelet count ≥ 100 × 10^9/L • Serum creatinine level > 200 µmol/L in case platelet count > 30 × 10^9/L • Known other causes of thrombocytopenia, e.g., enteric infection with E. coli 0157, atypical HUS, hematopoietic stem cell, bone marrow or organ transplantation–associated thrombotic microangiopathy, known or suspected sepsis, or diagnosis of disseminated intravascular coagulation • Congenital TTP • Clinically significant active bleeding or high risk of bleeding (excluding thrombocytopenia) • Known chronic treatment with anticoagulant treatment that could not be stopped safely, e.g., vitamin K antagonists, heparin or LMWH, non-ASA nonsteroidal anti-inflammatory molecules • Malignant arterial hypertension • Clinical condition other than that associated with TTP and a life expectancy of < 6 months • Known hypersensitivity to the active product or any excipient of the study drug • Patients who were previously enrolled in a clinical study with caplacizumab and received caplacizumab or for whom the assigned treatment arm was unknown
Drugs	**Intervention**	Caplacizumab adjunct to PEX plus glucocorticoids ± immunosuppressants (e.g., rituximab) Caplacizumab administration: • First day: Caplacizumab 10 mg[a] IV injection prior to PEX; caplacizumab 10 mg SC injection after completion of PEX • Subsequent days of treatment during PEX: Caplacizumab 10 mg SC injection q.d. following PEX • Subsequent days of treatment after PEX: Caplacizumab 10 mg SC injection q.d. for 30 days following the last daily PEX
	Comparator(s)	PEX plus glucocorticoids ± immunosuppressants (e.g., rituximab)
Duration	**Phase**	
	Screening	Not specified. From signing the informed consent form to randomization. Screening and baseline can be on the same day
	Double-blind	• Daily PEX period (variable duration depending on treatment response) • 30-day post–daily PEX period
	Treatment extension period	A 7- to 28-day extension with initial treatment allocation for patients with risks of TTP relapse
	Follow-up	4 weeks
Outcomes	**Primary end point**	Time to platelet count response (defined as "initial platelet count ≥ 150 × 10^9/L with discontinuation of daily PEX within 5 days thereafter")
	Secondary and exploratory end points	• Composite of TTP-related death, recurrence of TTP, or a thromboembolic event during the treatment period including extensions (composite end point) • Recurrence of TTP at various time points • Refractory TTP • Normalization of LDH, troponin, and serum creatinine • Clinically significant TTP-related events at various time points during the study (e.g., neurological events, cardiovascular events, exacerbation, relapse, death due to TTP)

		HERCULES
		• Platelet count • Mortality rate • Change from baseline in SMMSE total score at various timepoints • Platelet count at various timepoints • Time to stopping of daily PEX • Bleeding events • Number of days in ICU and in hospital • PEX parameters: number of days of PEX, volume of plasma exchanged • Immunogenicity • Safety
NOTES	**Publications**	Scully 2019[19]

aTTP = acquired thrombotic thrombocytopenic purpura; DB = double-blind; HUS = hemolytic uremic syndrome; ICU = intensive care unit; LMWH = low molecular weight heparin; PEX = plasma exchange; q.d. = once daily; RCT = randomized controlled trial; SC = subcutaneous; SMMSE = Standardized Mini-Mental State Examination; TTP = thrombotic thrombocytopenic purpura.

Note: One additional report was included (submission[3]).

[a] Even though the clinical trial protocol specified the caplacizumab dose as 10 mg, to be delivered by withdrawing all of the reconstituted solution from the vial and administering the full amount, a dose-recovery study showed that the mean dose that can be withdrawn from a vial is 11 mg, which is indicated in the product monograph for caplacizumab.[9]

Source: Clinical Study Report for HERCULES.[10]

Description of Studies

One double-blind, placebo-controlled RCT (HERCULES) identified from the literature search was included in this systematic review.[10] The objective of HERCULES was to evaluate the efficacy and safety of caplacizumab in adult patients with aTTP.

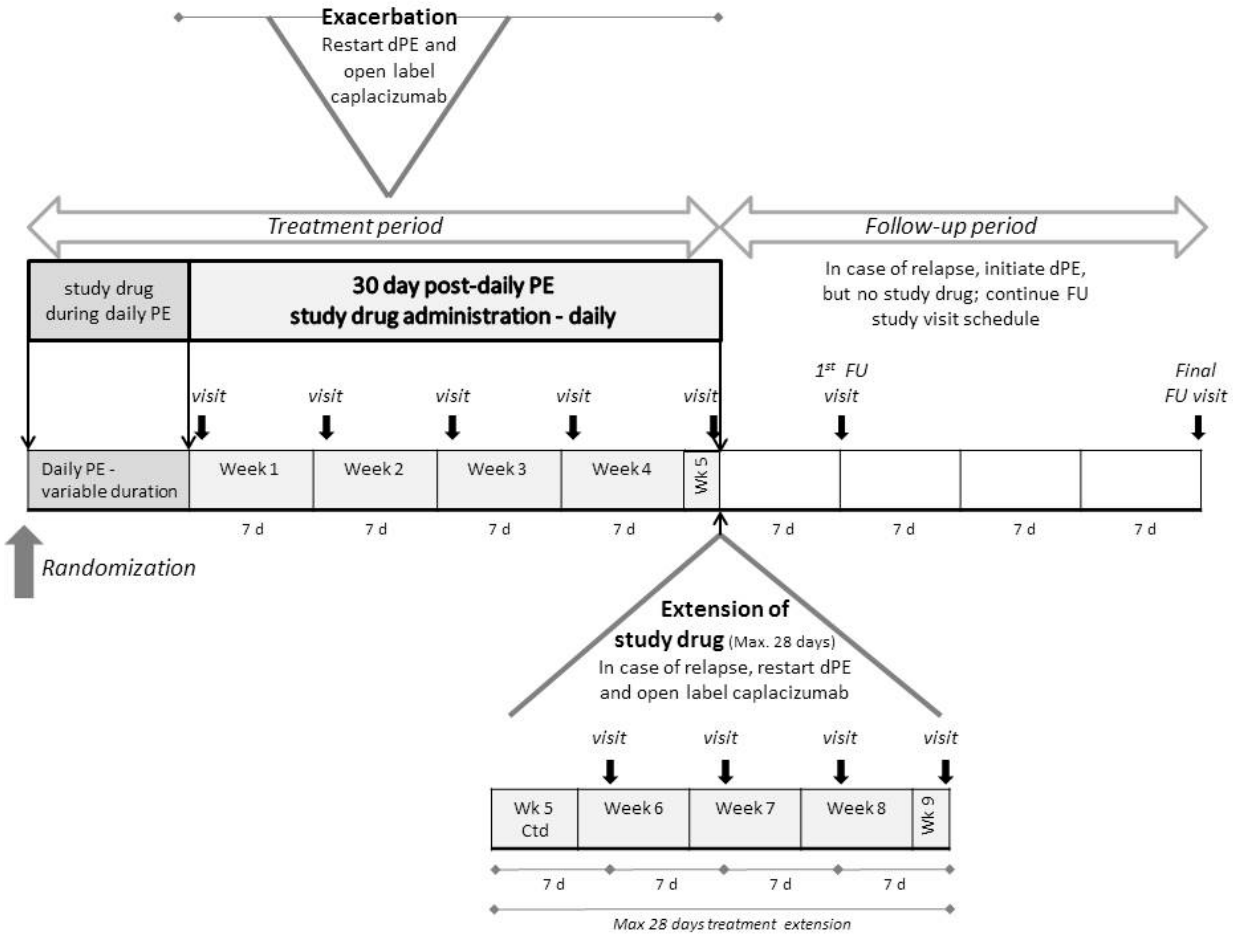
The overall study duration ranged from two to six months for each patient, which covered the following periods (Figure 2):

- Screening period: From the signing of the informed consent form until randomization (signing and randomization could occur on the same day).
- Double-blind treatment period: Consisting of the daily PEX period (variable duration) and the 30-day post–daily PEX period.
- Treatment extension period: Patients continued their assigned treatment for seven to 28 days if they were determined to have risk factors associated with relapse of the presenting TTP episode. This period had to be accompanied by an optimization of the immunosuppressive treatment.
- Open-label treatment period: Open-label treatment with caplacizumab, together with re-initiation of daily PEX and optimized immunosuppressive treatment, for patients who had an exacerbation during the 30-day treatment period or a relapse during the treatment extension period.
- Follow-up period: Four weeks after the last dose of the study drug.

After screening, eligible patients were randomized in a 1:1 ratio to receive caplacizumab or placebo, in addition to standard of care, which consisted of PEX and corticosteroid treatment, with or without immunosuppressants. Randomization was carried out via an interactive web or voice response system (IWRS/IVRS) and was stratified by the severity of neurological involvement (Glasgow Coma Scale [GCS] ≤ 12 versus GCS of 13 to 15). Investigative sites, patients, site monitors, and other members of the study team were

blinded to the treatment allocation until the final database lock, when the last patient has completed the final follow-up visit and all data are considered clean. At the end of the 30-day post–daily PEX period, if the investigator determined some patients had risk factors for relapse of the presenting TTP episode, they were allowed to extend their initially assigned treatment for seven to 28 days. Patients experiencing a first exacerbation during the 30-day post–daily PEX period (without a prior relapse), or a first relapse during the treatment extension period (without a prior exacerbation), were given open-label caplacizumab regardless of their initial treatment allocation, but the blind for the initial treatment allocation was not broken. In the case of unacceptable AEs, unblinding by the investigator was allowed via the IWRS/IVRS. Patients for whom unblinding had occurred had to discontinue treatment. The primary end point of the study was time to platelet count response. All samples were analyzed by a central laboratory, except for pregnancy testing, screening samples for creatinine assessment, and samples for platelet count. A data safety monitoring board consisting of an independent group of clinical experts and a statistician monitored the trial data.

Figure 2: Study Design for HERCULES



dPE = daily plasma exchange therapy; FU = follow-up; max = maximum; PE = plasma exchange; wk = week.

Source: Clinical Study Report for HERCULES.[10]

Populations

Inclusion and Exclusion Criteria

Adult patients (≥ 18 years of age) with a clinical diagnosis of aTTP presenting with both thrombocytopenia and microscopic evidence of red blood cell fragmentation were enrolled in HERCULES. The participants were required to have initiated daily PEX and received one PEX treatment prior to randomization. The maximum time allowed between the start of the first PEX and the start of the first PEX after randomization was 24 hours. Patients were excluded if they had platelet counts greater than 100 × 10^9/L at screening, had suspected thrombotic microangiopathies that were not associated with aTTP (such as hemolytic uremic syndrome), or if they had congenital TTP. Patients who had clinically significant active bleeding or a high risk of bleeding, or receiving chronic treatment with anticoagulant treatment that could not be stopped safely were also excluded. Details of the inclusion and exclusion criteria in HERCULES are provided in Table 3.

Baseline Characteristics

In HERCULES, patient characteristics were generally similar between groups at baseline (Table 4). The mean age of the patients was 45 to 47 years. Most patients were female (68% to 70%) and white (68% to 78%). The mean platelet count at baseline was 32 × 10^9/L to 39 × 10^9/L, and 82% to 90% of the patients had an ADAMTS13 activity of 10% or less. More patients in the caplacizumab group had no previous TTP episode (67% in the caplacizumab group versus 47% in the placebo group), but were determined to have very severe disease (42% in the caplacizumab group versus 34% in the placebo group). Severity of disease in HERCULES was assessed using the French severity score, which is a discrete score ranging from 0 to 4 involving the evaluation of three parameters: cerebral involvement ([yes = 1, no = 0]; LDH [> 10 × the upper limit of normal [ULN] = 1, ≤ 10 × ULN = 0]; and age [> 60 years = 2, > 40 and ≤ 60 years = 1, ≤ 40 years = 0]), severe neurological involvement (e.g., coma, seizures, focal deficit), and cardiac involvement (based on cTnI).

Patients in the caplacizumab group reported higher cTnI levels and higher LDH levels at baseline compared with those in the placebo group. More patients in the placebo group ([redacted]) had thromboembolic events compared with those in the caplacizumab group ([redacted]).

Table 4: Summary of Baseline Characteristics, ITT Population

Characteristics	HERCULES	
	Caplacizumab (N = 72)	Placebo (N = 73)
Age, years, mean (SD)	44.9 (13.5)	47.3 (14.1)
Sex, n (%)		
Male	23 (31.9)	22 (30.1)
Female	49 (68.1)	51 (69.9)
Race, n (%)		
White	47 (68.1)	50 (78.1)
Black or African American	15 (21.7)	13 (20.3)
Asian	4 (5.8)	0
Native Hawaiian or other Pacific Islander	1 (1.4)	0
Other	2 (2.9)	1 (1.6)

Characteristics	HERCULES	
	Caplacizumab (N = 72)	Placebo (N = 73)
Missing	3	9
Baseline platelet count, × 10^9/L, mean (SD)	32.0 (27.2)	39.1 (29.1)
Previous TTP episodes, n (%)		
Initial	48 (66.7)	34 (46.6)
Recurrent	24 (33.3)	39 (53.4)
Number of previous TTP episodes, n (%)		
0	48 (66.7)	34 (46.6)
1	8 (11.1)	21 (28.8)
2	9 (12.5)	7 (9.6)
> 2	7 (9.7)	11 (15.1)
Severity of disease, n (%)[a]		
Very severe	30 (41.7)	25 (34.2)
Less severe	42 (58.3)	48 (65.8)
ADAMTS13 activity, n (%)		
< 10%	58 (81.7)	65 (90.3)
≥ 10%	13 (18.3)	7 (9.7)
Missing	1	1
cTnI		
Mean (SD), mcg/L	3.47 (13.6)	0.63 (1.6)
≤ ULN, n (%)	[redacted]	[redacted]
> ULN, n (%)	[redacted]	[redacted]
Missing	[redacted]	[redacted]
LDH		
Mean (SD), U/L	[redacted]	[redacted]
≤ ULN, n (%)	[redacted]	[redacted]
> ULN, n (%)	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Serum creatinine		
Mean (SD), µmol/L	[redacted]	[redacted]
≤ ULN, n (%)	[redacted]	[redacted]
> ULN, n (%)	[redacted]	[redacted]
Missing	[redacted]	[redacted]
GCS score, n (%)		
≤ 12	6 (8.5)	5 (6.9)
13 to 15	65 (91.5)	67 (93.1)
Missing	1	1
SMMSE total score, mean (SD)	24.8 (8.9)	25.3 (6.3)
vWF:Ag concentration, %, mean (SD)	159.49 (52.4)	174.52 (79.8)
TTP-related medical history, n (%)		

Characteristics	HERCULES	
	Caplacizumab (N = 72)	Placebo (N = 73)
Thromboembolic events	[redacted]	[redacted]
Splenectomies	[redacted]	[redacted]
Hypothyroidism or taking thyroid hormones	[redacted]	[redacted]

ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; cTnI = cardiac troponin I; DB = double-blind; GCS = Glasgow Coma Scale; ITT = intention-to-treat; LDH = lactate dehydrogenase; SD = standard deviation; SMMSE = Standardized Mini-Mental State Examination; TTP = thrombotic thrombocytopenic purpura; U/L = units per litre; ULN = upper limit of normal; vWF:Ag = von Willebrand factor antigen.

[a] Severity of disease was assessed using the French severity score, a discrete score from 0 to 4 involving evaluation of three parameters: cerebral involvement ([yes = 1, no = 0], LDH [> 10 × ULN = 1, ≤ 10 × ULN = 0], and age [> 60 years = 2, > 40 years and ≤ 60 years = 1, ≤ 40 years = 0]), severe neurological involvement (e.g., coma, seizures, focal deficit), and cardiac involvement (based on cTnI).

Source: Clinical Study Report for HERCULES.[10]

Interventions

After screening, eligible study participants were randomized in a ratio of 1:1 to receive caplacizumab or placebo in addition to standard-of-care therapy.

The double-blind treatment consisted of two periods: the daily PEX period and the 30-day post–daily PEX period. A treatment extension with open-label caplacizumab was allowed for patients with risk factors for relapse of the presenting TTP episode.

On the first day of the double-blind daily PEX period, patients received a loading dose of caplacizumab 10 mg or placebo by IV bolus injection prior to PEX. From day 1 and throughout the daily PEX period, caplacizumab 10 mg or placebo subcutaneous injection was given once a day within two hours after the end of PEX therapy. Patients were hospitalized for the duration of the daily PEX period.

After stopping PEX, treatment with caplacizumab 10 mg or placebo subcutaneous injection once a day continued for 30 days following the last daily PEX. During this period, patients were discharged from hospital and caplacizumab or placebo was self-administered by the patient or a caregiver. Patients or caregivers were given training on proper injection technique.

Administration of caplacizumab or placebo could be extended for an additional seven to 28 days for patients who had persistent active underlying disease (and risk factors for relapse of aTTP had been identified, in the opinion of the investigator). The risk factors for relapse of the presenting aTTP episode included persistent severe ADAMTS13 deficiency and the presence of ADAMTS13 inhibitors, as well as other signs and symptoms of continued underlying disease activity. Clinicians could also optimize the immunosuppressive treatment by reversing corticosteroid tapering or restarting corticosteroid treatment, or by starting or continuing rituximab. Study drug treatment extension was stopped when ADAMTS13 activity showed a sustained upward trend greater than 10% or was stable, when there were no other signs and symptoms of disease activity, or on day 28 of the study drug treatment extension (at the latest).

During the study, in the case of the first exacerbation of the presenting TTP episode (during the 30-day post–daily PEX period) or a first relapse (during the treatment extension period, without a prior exacerbation), patients would receive open-label caplacizumab together with daily PEX, irrespective of what the initial treatment allocation was. There was no re-initiation of caplacizumab for patients experiencing more than one exacerbation or relapse and, in that case, the standard-of-care treatment of daily PEX and appropriate immunosuppressive

treatment was initiated, as per site practice. For a TTP recurrence that occurred during the four-week follow-up period after the completion of the study drug treatment, the standard-of-care treatment of daily PEX and appropriate immunosuppressive treatment was initiated as per site practice, without re-initiation of the study drug.

Standard-of-care therapy included PEX (e.g., fresh frozen plasma, solvent detergent-inactivated or viral-inactivated plasma, or cryosupernatant) and corticosteroid treatment. PEX (1 to 1.5 times the estimated plasma volume) should have been started prior to randomization, with volume and intensity at the discretion of the investigator. After randomization, PEX duration and whether the desired volume was exchanged in one or more sessions within 24 hours was at the discretion of the investigator, according to standard site practice. Once the platelet count was greater than or equal to 150×10^9/L, daily PEX needed to continue for at least two days. Tapering of PEX after platelet count normalization, defined as reducing its frequency to less than once per day, was strongly discouraged and, if considered, was to be discussed with the medical monitor.

Corticosteroid treatment had to be initiated or continued with a prednisolone or prednisone regimen of at least 1 mg/kg/day IV or orally during the daily PEX period and continued for the first week after the end of daily PEX. 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 PEX, as clinically indicated. At the week 3 visit of the 30-day post–daily PEX period, corticosteroid tapering had to be reassessed based on the ADAMTS13 activity data of the previous two visits and other clinical signs of underlying disease.

The use of other immunosuppressive treatments, such as rituximab, was permitted per standard site practice but had to be considered in light of protocol required corticosteroid treatment.

The existing use of anticoagulant treatment, such as vitamin K antagonists, heparin, or low molecular weight heparin, needed to be stopped prior to the patient's inclusion in the study. If needed, anticoagulant treatment could be restarted at the discretion of the investigator but had to be used with caution.

Outcomes

Survival

Deaths (all causes and TTP-related) that occurred during the double-blind treatment daily PEX period, overall treatment period, follow-up period, and the overall study period were reported in HERCULES. In addition, TTP-related death was one component of a composite end point that included TTP-related death, recurrence of TTP, or a thromboembolic event during the treatment period. The composite end point was one of the key secondary end points in HERCULES.

Reduction in Use of PEX

Time to stopping of daily PEX, the number of days of PEX, and the total PEX volume were secondary efficacy end points in HERCULES.

Time to stopping of daily PEX was derived as the date the daily PEX was stopped minus the date of the first IV loading dose of the study drug after randomization, plus one day. The number of PEX days was defined as the total number of days on which PEX was documented. The total PEX volume was calculated by the PEX volume, summed over all PEX days. Results in the double-blind treatment daily PEX period and the overall treatment

period were reported. Patients were analyzed according to their initial treatment group, both before and after the switch to open-label caplacizumab. Two treatment groups were used for data analysis:

- caplacizumab plus open-label caplacizumab
- placebo plus open-label caplacizumab

aTTP Recurrence

An aTTP relapse was a TTP recurrence that occurred after the 30-day post–daily PEX period. An aTTP exacerbation was a TTP recurrence that occurred during the first 30 days after the daily PEX period. See "platelet counts" for a more detailed description. TTP recurrence was one of the key secondary end points in HERCULES. It was also one component of a composite end point (key secondary end point) that included TTP-related death, recurrence of TTP, or a thromboembolic event during the treatment period.

Organ Damage Markers

Time to first normalization of all three organ damage marker levels (LDH, cTnI, and serum creatinine) was one of the key secondary end points in HERCULES. This outcome was calculated by taking the first time that LDH, cTnI, and serum creatinine were less than or equal to the ULN and subtracting the time of the first IV loading dose of the study drug after randomization, plus one minute.

Time to normalization of LDH, cTnI, or serum creatinine was classified under "other secondary efficacy end points." A separate Kaplan-Meier analysis for each organ damage marker was conducted (time to LDN ≤ 1 × ULN, time to cTnI ≤ 1 × ULN, and time to serum creatinine ≤ 1 × ULN). These outcomes were calculated by taking the first time the organ damage marker was less than or equal to the ULN and subtracting the time of the first IV loading dose of the study drug after randomization, plus one minute.

Prevention of Major Thromboembolic Events

The proportions of patients with major thromboembolic events, such as myocardial infarction, cerebrovascular accident, pulmonary embolism, or deep vein thrombosis, were reported in HERCULES. This outcome was also one component of a composite end point that included TTP-related death, recurrence of TTP, or a thromboembolic event during the treatment period. The composite end point was one of the key secondary end points in HERCULES.

Prevention of Refractory aTTP to Treatment

The proportions of patients with refractory aTTP during the study were reported in HERCULES. Refractory aTTP was defined as the lack of a doubling of the platelet count after four days of treatment (i.e., platelet count after four days of standard treatment divided by the count at start of treatment is < 2) and an LDH greater than the ULN after four days of standard treatment. This was one of the key secondary outcomes in HERCULES. Refractory aTTP, as defined according to Scully et al.,[20] was a secondary efficacy end point. In this study, refractory aTTP was defined as a lack of a sustained platelet count increment or platelet counts less than 50×10^9/L and persistently raised LDH (> 1.5 × ULN), despite five PEXs and steroid treatment.

Response to Treatment

Time to platelet count response was the primary efficacy end point in HERCULES. Platelet count response was defined as an initial platelet count of 150 × 10^9/L or higher with the subsequent stopping of daily PEX within five days of treatment.

Platelet Counts

The number of patients with platelet counts of 150 × 10^9/L or higher at the end of the study drug treatment periods was measured. This was a secondary efficacy end point in HERCULES.

Several outcome measures in HERCULES were defined based on platelet counts:

- **Platelet count response**: This was the primary efficacy outcome in HERCULES and was reported as time to platelet count response. Platelet count response was defined as an initial platelet count of 150 × 10^9/L or higher with the subsequent stopping of daily PEX within five days of treatment.
- **Recurrence** (exacerbation and relapse): This was defined as a TTP episode (TTP recurrence was also one component of a composite end point that included TTP-related death, recurrence of TTP, or a thromboembolic event) during the treatment period. The composite end point was one of the key secondary end points in HERCULES.
  - **Exacerbation**: This was defined as recurrent thrombocytopenia after initial recovery of platelet count (platelet count ≥ 150 × 10^9/L with subsequent stopping of daily PEX within five days) requiring re-initiation of daily PEX. Exacerbation occurred during the first 30-day post–daily PEX period.
  - **Relapse**: This was defined as recurrent thrombocytopenia after initial recovery of platelet count requiring re-initiation of daily PEX. TTP relapse occurred after the 30-day post–daily PEX period when caplacizumab was discontinued.
- **Refractory TTP**: This was defined as the absence of platelet count doubling after four days of standard treatment and an LDH greater than the ULN.

Neurological Assessment

The proportion of patients with neurological symptoms based on neurological assessment on days 1, 2, 3, 4, and 5 and weeks 1 and 5 of the 30-day post–daily PEX treatment period and the follow-up period was summarized by treatment group (caplacizumab, placebo, open-label caplacizumab) in HERCULES. This was a secondary efficacy end point.

Cognitive Assessment

Actual value and change from baseline in the Standardized Mini-Mental State Examination (SMMSE) total score on days 1, 2, 3, 4, and 5 and weeks 1 and 5 of the 30-day post–daily PEX treatment period and the follow-up period were summarized by treatment group (caplacizumab, placebo, open-label caplacizumab) in HERCULES. This was a secondary efficacy end point.

The SMMSE is a widely used instrument for assessing cognitive impairment in older adults.[21,22] Multiple domains of cognitive function are evaluated, including orientation to time and place, registration, concentration, short-term recall, naming familiar items, repeating a common expression, and ability to read and follow instructions.[21] The SMMSE is scored based on a 30-point questionnaire. Among the general population, a score of 26 to 30 is considered normal, 20 to 25 indicates possible mild cognitive impairment, 10 to 20 is considered moderate cognitive impairment, and 0 to 9 corresponds to severe cognitive impairment. A minimal clinically important difference (MCID) was not identified for the

general population or patients with aTTP, although the clinical experts consulted on this review indicated that an MCID of one to two points is commonly used for patients with dementia, Alzheimer disease, and other neurodegenerative diseases. Details of the SMMSE are provided in Appendix 4.

Hospitalization Due to aTTP Episodes

Number of days in ICU and in hospital were summarized by treatment group in the double-blind treatment daily PEX period, in the overall treatment period, in the follow-up period, and in the overall study period. Patients were analyzed according to their initial treatment group, regardless whether a patient was switched to open-label caplacizumab. These two treatment groups were used for data analysis:

- caplacizumab plus open-label caplacizumab
- placebo plus open-label caplacizumab

The number of days in ICU was calculated as ICU discharge date minus ICU admission date plus one day, summed over all stays in the ICU. The number of days in hospital was calculated as discharge date minus admission date plus one day, summed over all hospitalizations, including days in the ICU.

Safety

TEAEs, SAEs, withdrawals due to adverse events (WDAEs), and AEs of special interest were reported. Of note, all exacerbations and relapses had to be reported as SAEs. AEs of special interest were pre-specified in the study protocol.

Statistical Analysis

The sample size in HERCULES was calculated using a two-sided log-rank test with a significance level of 0.05. The determination of sample size was based on the assumption that patients in the caplacizumab arm would observe a 40% reduction in the time to platelet count response compared with placebo. When the time to response in the placebo arm was assumed to be seven days, the median time to response in the caplacizumab arm would be 4.2 days. In addition, an assumed dropout rate of 10% in the first 10 days after first administration of the study drug was taken into account in the sample size calculation. Given these assumptions, a total sample size of 132 patients would provide 80% power to detect a difference in the median time to platelet response between treatment groups. Furthermore, the sponsor stated that the planned sample size could provide 83% power to detect a 20% reduction in the first key secondary end point (composite of TTP-related death, recurrence of TTP, or a thromboembolic event), using a two-sided chi-squared test with a large sample approximation and a 5% significance level, given the assumption of incidence of 10% and 30% in the caplacizumab and placebo arms, respectively.

In general, for continuous parameters, descriptive statistics, such as the arithmetic mean, the standard deviation (SD) for baseline summaries or SE for post-baseline or change from baseline summaries, the median, minimum, and maximum were presented. For categorical parameters, frequency and percentages of the events were presented.

During the PEX therapy, platelet counts, organ damage markers, clinically significant TTP events, neurologic assessment, cognitive assessment, and bleeding assessment were conducted daily until the end of the daily PEX. After stopping PEX, weekly assessments were performed on days 8, 15, 22, and so on. During the 30-day post–daily PEX period, organ damage markers, ADAMTS13 activity, clinically significant TTP events, and bleeding

events were evaluated weekly, while neurologic assessment, cognitive assessment, and anti-drug antibody assessment were conducted on day 1 and day 30 of this period. During the follow-up period, all clinical assessments and laboratory analyses were performed seven and 28 days after the last dosing of the study drug.

The overall treatment period consisted of a double-blind treatment period and might have included an extension treatment period or an open-label treatment period, if needed. Different methods were used for the analyses of different efficacy outcomes. For example, during the double-blind treatment period, for patients who experienced an exacerbation or relapse and were switched to open-label caplacizumab, only data up to the switch were used in the analyses of these treatment groups. For patients who had refractory aTTP, data before and after the switch were analyzed, based on their initial treatment (placebo) arm only. For analyses of the open-label caplacizumab treatment group, only data collected after the switch to open-label caplacizumab were used.

In general, there was no imputation of missing values, unless otherwise specified. When computing percentages, missing values were not included in the denominator count.

There was no interim analysis in this study.

Primary Outcome(s) of the Studies

The primary efficacy outcome in HERCULES was time to platelet count response, defined as an initial platelet count of 150×10^9/L or higher with discontinuation of daily PEX within five days. A two-sided stratified log-rank test based on a Kaplan-Meier analysis, with severity of neurological involvement (GCS score ≤ 12 versus 13 to 15), was conducted to compare the time to platelet count response between treatment groups. Data were also analyzed using a Cox proportional hazards regression model with time to platelet count response as the dependent variable, and treatment group and GCS category as independent variables. The hazard ratio from the Cox model was reported along with corresponding 95% CIs. The primary efficacy analysis was performed in the ITT population.

In the primary efficacy analysis, no imputation of missing data was made. Sensitivity analyses were conducted for the primary end point to assess the impact of various analysis sets (e.g., mITT population and per-protocol population).

Subgroup analyses based on ADAMTS13 activity at baseline (< 10% versus ≥ 10%), previous TTP episodes (initial versus recurrent), and severity of disease at baseline (very severe versus less severe) was performed for the primary efficacy outcome.

Secondary Outcomes of the Studies

All analyses on the key secondary outcomes were run on the ITT population.

HERCULES used a pre-specified ordered testing procedure to control for inflated type I error rates. Four key secondary end points were hierarchically ordered. To advance to the next test (e.g., from test 1 to test 2, from test 2 to test 3, and so on), the preceding test criterion must be met (e.g., the corresponding null hypothesis must be rejected). If the corresponding null hypothesis was not rejected, the testing was stopped and no further conclusions could be drawn.

The statistical testing hierarchy was as follows:

1. Proportion of patients with TTP-related death, a recurrence of TTP, or at least one treatment-emergent major thromboembolic event during the overall treatment period,

including extensions: A Cochran-Mantel-Haenszel test was conducted with adjustment for GCS category (indicating severity of neurological involvement, a stratification factor used in randomization). For both treatment groups, only events that had occurred prior to a switch to open-label caplacizumab were evaluated for this analysis.

2. Proportion of patients with aTTP recurrence (defined as exacerbation or relapse, depending on the timing of recurrence) in the overall study period including the four-week follow-up period: A Cochran-Mantel-Haenszel test was conducted with adjustment for GCS category. For both treatment groups, only recurrences that had occurred prior to a potential switch to open-label caplacizumab were evaluated for this analysis.
3. Proportion of patients with refractory aTTP (defined as absence of platelet count doubling after four days of standard treatment and LDH > ULN): A Cochran-Mantel-Haenszel test with adjustment for GCS category was conducted. Patients who had crossed over to open-label caplacizumab were analyzed in the initial treatment arm (placebo) only. Patients who were discontinued because they were lost to follow-up or withdrew consent before day 5 were excluded from the analysis. Missing values in the analyses for refractory aTTP were imputed by using multiple imputation (Markov chain Monte Carlo) using simulated average parameter values.
4. Time to normalization of all three organ damage markers (LDH, cTnI, and serum creatinine): among patients with at least one abnormal biomarker at baseline, a stratified log-rank test was conducted based on a Kaplan-Meier analysis with adjustment for GCS category and for an additional factor defining whether the patient had abnormal values at baseline for LDH only (not for cTnI or for serum creatinine). Patients in either initial treatment group who had switched to open-label caplacizumab before having reached the end point were censored at time of switch. All on-treatment records during the double-blind treatment period were included in the analysis.

Other secondary efficacy end points were summarized using descriptive statistics such as the number of observations, means, SEs, and proportions as appropriate. All analyses on other secondary end points were run on the ITT population.

Analysis Populations

The ITT population included all patients who were randomized, also called the as-randomized set. This was the primary population for efficacy analyses.

The mITT population included all randomized patients who received at least one administration of the study drug, as randomized. The mITT population was used for a selected sensitivity analysis of efficacy.

The per-protocol population was a subpopulation of the ITT population that excluded those patients who had a major protocol deviation. A sensitivity analysis of the primary efficacy outcome was performed on the per-protocol population.

The safety population was defined as all patients who received at least one administration of the study drug as treated, also called the as-treated set. This population was used for analysis of safety, disease markers, and immunogenicity data.

The open-label caplacizumab population referred to all patients who received at least one administration of the open-label study drug. This population was used in cases where a separate analysis of the open-label period was performed.

Results

Patient Disposition

In HERCULES, of a total of 149 patients who were screened, 145 were randomized to receive either caplacizumab (n = 72) or placebo (n = 73). One patient in the caplacizumab group withdrew consent prior to the first dosing. Three patients in the caplacizumab group and 28 patients in the placebo group experienced a disease recurrence during the double-blind treatment period. Among those had an aTTP recurrence, two patients in the caplacizumab group and 26 in the placebo group were switched to the open-label caplacizumab therapy. The proportion of patients who completed the overall study period, including the follow-up period, was higher in the caplacizumab group (81%) compared with the placebo group (69%). The main reason for premature study discontinuation was AEs, and the rates of AEs leading to treatment discontinuation were similar in the two treatment groups: 8% in the caplacizumab group, and 7% in the placebo group. Other main reasons for study discontinuation were withdrawal of consent and physician's decision.

Details of patient disposition for HERCULES are provided in Table 5.

Table 5: Patient Disposition

	HERCULES	
	Caplacizumab	Placebo
Screened, N	149	
Randomized	72	73
Experienced a recurrence during DB period, n (%)	3 (4.1)	28 (38.4)
Discontinued the study at time of recurrence	1	2
Switched to OL caplacizumab treatment, n (%)	2 (2.8)	26 (35.6)
Discontinued OL period	1	7
Completed 30-day post–daily PEX period, n (%)	60 (83.3)	33 (45.2)
Entered the 1- to 4-week treatment extension, n (%)	20 (27.8)	5 (6.8)
Entered the follow-up period, n (%)	[redacted]	[redacted]
Completed overall study period, n (%)	[redacted]	[redacted]
Discontinued from the study, n (%)	14 (19.4)	23 (31.5)
Primary reason for discontinuation, n (%)		
Adverse events	6 (8.3)	5 (6.8)
Lost to follow-up	0	1 (1.4)
Non-compliance with study drug	0	1 (1.4)
Patient or legal representative withdrew consent	4 (5.6)	6 (8.2)
Physician's decision	2 (2.8)	4 (5.5)
Death	1 (1.4)	3 (4.1)
Other	1 (1.4)	3 (4.1)
ITT, n (%)	72 (100)	73 (100)
mITT, n (%)	[redacted]	[redacted]
PP, n (%)	41 (56.9)	40 (54.8)
Safety, n (%)	71 (98.6)	73 (100)

	HERCULES	
	Caplacizumab	Placebo
OL caplacizumab, n (%)	2 (2.8)	26 (35.6)

DB = double-blind; ITT = intention-to-treat; mITT = modified intention-to-treat; OL = open-label; PEX = plasma exchange; PP = per-protocol.

Source: Clinical Study Report for HERCULES.[10]

Exposure to Study Treatments

Extent of exposure was based on the safety population and calculated as:

- Double-blind duration (days) = Date of last administration minus date of first administration within the double-blind treatment period plus one.
- Open-label treatment duration (for switchers only) (days) = Date of last administration minus date of first administration within the open-label treatment period plus one.

During the double-blind treatment period, which consisted of a daily PEX period and a 30-day post–daily PEX period, the median duration of treatment with the study drug was 35 days in the caplacizumab group and 23 days in the placebo group. For patients switched to open-label caplacizumab, the median duration of treatment was 37 days. Details of patient exposure to study treatments in HERCULES are provided in Table 6.

Table 6: Extent of Exposure, Safety Population

	HERCULES	
	Caplacizumab (n = 71)	Placebo (n = 73)
Exposure to study drugs		
DB treatment period		
Duration of study drug treatment, days, median (minimum; maximum)	35 (1; 65)	23 (2; 66)
OL treatment period		
Duration of study drug treatment, days, median (minimum; maximum)	36.5 (3; 65)	NA
Exposure to corticosteroids or rituximab		
Immunosuppressive medications taken during the overall study period, n (%)	70 (97.2)	71 (97.3)
Corticosteroids	69 (98.6)	71 (100)
Rituximab	28 (40.0)	35 (49.3)
Other	13 (18.6)	4 (5.6)
Immunosuppressive medications taken during the DB daily PEX period, n (%)	[redacted]	[redacted]
Corticosteroids	[redacted]	[redacted]
Rituximab	[redacted]	[redacted]
Immunosuppressive medications taken during the DB post–daily PEX period, n (%)	[redacted]	[redacted]
Corticosteroids	[redacted]	[redacted]
Rituximab	[redacted]	[redacted]
Immunosuppressive medications taken during the OL daily PEX period, n (%)	[redacted]	[redacted]
Corticosteroids	[redacted]	
Rituximab	[redacted]	
Immunosuppressive medications taken during the OL post–daily PEX period, n (%)	[redacted]	[redacted]
Corticosteroids	[redacted]	
Rituximab	[redacted]	
Immunosuppressive medications taken during the follow-up period, n (%)	[redacted]	[redacted]
Corticosteroids	[redacted]	[redacted]

	HERCULES	
	Caplacizumab (n = 71)	Placebo (n = 73)
Rituximab	[redacted]	[redacted]

DB = double-blind; NA = not applicable; OL = open-label; PEX = plasma exchange.

Source: Clinical Study Report for HERCULES.[10]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported subsequently.

Survival

Three patients in the placebo group compared with no patients in the caplacizumab group died during the daily PEX treatment period. All deaths were considered by the independent adjudication committee to be TTP-related. Two of the deaths were considered by the investigator to be possibly related to the study drug, and the third death was considered not related. None of the deaths were considered by the investigator to be related to corticosteroids or PEX.

In the caplacizumab group, no patients died during the treatment period. One patient died during the follow-up period; this death was assessed as TTP-related by the adjudication committee. The investigator considered the death not related to the study drug or corticosteroid.

Details of mortality are provided in Table 7.

The sponsor provided an integrated efficacy analysis that included all randomized patients in HERCULES and TITAN (a phase II, single-blind RCT comparing caplacizumab with placebo in patients with aTTP; details are provided in Other Relevant Evidence).[23] The results showed that treatment with caplacizumab was associated with a statistically significant reduction in mortality rates. There were six deaths during the entire study period: one patient (0.9%) in the caplacizumab groups and five patients (4.5%) in the placebo groups. Details are provided in Appendix 3.

Table 7: Mortality – ITT Population, Overall Study Period

	HERCULES	
	Caplacizumab (n = 71)	Placebo (n = 73)
Number of patients analyzed	71	73
DB treatment period, daily PEX therapy	0	3 (4.1)
DB treatment period, 30-day post–daily PEX therapy	0	0
OL treatment period	0	0
Follow-up period	1 (1.5)	0
Overall study treatment period	1 (1.4)	3 (6.4)

DB = double-blind; ITT = intention-to-treat; OL = open-label; PEX = plasma exchange.

Note: The percentage of death was calculated based on the number of patients available. Although an ITT population was specified, the number of patients in the caplacizumab group was reported as 71.

Source: Clinical Study Report for HERCULES.[10]

Reduction in Use of PEX

Patients were analyzed according to their initial treatment allocation for this outcome.

During the daily PEX treatment period, the number of days on PEX was similar between two treatment groups ([redacted]). Treatment with caplacizumab was associated with reduced total PEX volume compared with placebo; the mean total PEX volume was [redacted], respectively. According to the clinical experts consulted for this review, the between-group difference in the PEX volume was clinically relevant.

During the overall treatment period, treatment with caplacizumab was related to a shorter duration of PEX therapy compared with placebo (mean days on PEX: 5.8 [SE = 0.5] for caplacizumab and 9.4 [SE = 0.8] for placebo). Treatment with caplacizumab was also associated with a reduced total PEX volume compared with placebo (21.3 [SE = 1.6] litres versus 35.9 [SE = 4.2] litres, respectively). According to the clinical experts consulted for this review, the between-group difference in the PEX volume was clinically relevant.

The clinical experts consulted on this review indicated that a one-day difference in the number of PEX days would not be considered a clinically meaningful change; whereas, a three-day difference is clinically relevant.

Details of the change in use of PEX are presented in Table 8.

Table 8: Use of PEX, Intention-to-Treat Population

	HERCULES	
	Caplacizumab (n = 72)	Placebo (n = 73)
Number of days of PEX, daily PEX period		
Number of patients analyzed	71	73
Days, mean (SE)	[redacted]	[redacted]
Days, median (range)	[redacted]	[redacted]
Number of days of PEX, overall treatment period including OL period		
Number of patients analyzed	71	73
Days, mean (SE)	5.8 (0.51)	9.4 (0.81)
Days, median (range)	5 (1 to 35)	7 (3 to 46)
Total volume of PEX, daily PEX period		
Number of patients analyzed	71	73
L, mean (SE)	[redacted]	[redacted]
L, median (range)	[redacted]	[redacted]
Total volume of PEX, overall treatment period, including OL period		
Number of patients analyzed	71	73
L, mean (SE)	21.33 (1.62)	35.93 (4.17)
L, median (range)	18.06 (5.3 to 102.2)	26.94 (4.0 to 254.0)

OL = open-label; PEX = plasma exchange; SE = standard error.

Source: Clinical Study Report for HERCULES.[10]

Recurrence of aTTP: aTTP Relapse

Recurrence of aTTP, either a relapse or exacerbation, was measured in different study periods. Relapses occurred after the 30-day post–daily PEX period. In HERCULES, relapse was one component of a composite outcome (ranked first in the statistical test hierarchy, including TTP-related death, recurrence of aTTP, and treatment-emergent major thromboembolic event), and only relapses during the overall treatment period were taken into account in the assessment of this composite outcome. The proportion of patients with a recurrence of aTTP was also assessed alone as a key secondary outcome in the overall study period, including the follow-up period, and ranked second in the statistical test hierarchy.

During the overall study period, a statistically significantly lower percentage of patients in the caplacizumab group (nine patients, 12.7%) compared with the placebo group (28 patients, 38.4%) experienced recurrence of aTTP (an exacerbation or relapse) (P = 0.0004). The lower recurrence of aTTP in the caplacizumab group was driven by lower exacerbations in this group.

During the overall treatment period covering the double-blind daily PEX therapy period and the 30-day post–daily PEX period, fewer patients in the caplacizumab group (three patients [4.2%]) reported aTTP recurrence (exacerbations) compared with the placebo group (28 patients, 38.4%).

During the follow-up period, six patients (9.1%) in the caplacizumab group had an aTTP recurrence (relapse) compared with no patients in the placebo group.

Details of aTTP recurrence are presented in Table 9.

Table 9: Recurrence of aTTP in the ITT Population – Overall Study Period, DB Treatment Period, and Follow-Up Period

	HERCULES	
	Caplacizumab (n = 72)	Placebo (n = 73)
Number of patients analyzed	71	73
Recurrence of aTTP during overall study period (relapse or exacerbation), n (%)	9 (12.7)	28 (38.4)
P value for caplacizumab versus placebo	P = 0.0004	
Number of patients analyzed	71	73
Recurrence of aTTP during DB treatment period (exacerbation), n (%)	3 (4.2)	28 (38.4)
Number of patients analyzed	66	NR
Recurrence of aTTP during follow-up (relapse), n (%)	6 (9.1)	0

aTTP = acquired thrombotic thrombocytopenic purpura; DB = double-blind; ITT = intention-to-treat; NR = not reported.

Note: P value of Cochran-Mantel-Haenszel test comparing caplacizumab with placebo adjusted for Glasgow Coma Scale score at randomization.

Source: Clinical Study Report for HERCULES.[10]

Recurrence of aTTP: aTTP Exacerbation

This outcome was one component of a composite end point (TTP-related death, recurrence of aTTP, or at least one treatment-emergent major thromboembolic event). During the overall treatment period that covered the double-blind daily PEX therapy and 30-day post–

daily PEX therapy, the risk of aTTP exacerbation was lower in the caplacizumab group (three patients [4.2%]) compared with the placebo group (28 patients [38.4%]). The statistically significant between-group difference (P < 0.0001) in the composite end point was largely driven by aTTP exacerbation.

Details of the aTTP exacerbation and the composite end point are provided in Table 10.

Table 10: TTP-Related Death, Recurrence of TTP, or One or More Treatment-Emergent Major Thromboembolic Events – ITT Population, Overall Treatment Period

	HERCULES	
	Caplacizumab (n = 72)	Placebo (n = 73)
Number of patients analyzed	71	73
TTP-related death, n (%)	0	3 (4.1)
Recurrence of TTP (exacerbation), n (%)	3 (4.2)	28 (38.4)
≥ 1 treatment-emergent major thromboembolic event, n (%)	6 (8.5)	6 (8.2)
Total,[a] n (%)	9 (12.7)	36 (49.3)
P value for caplacizumab versus placebo	P < 0.0001[b]	

GCS = Glasgow Coma Scale; ITT = intention-to-treat; TTP = thrombotic thrombocytopenic purpura.

[a] At least one of the following: TTP-related death, recurrence of TTP, or one or more treatment-emergent major thromboembolic events.

[b] P value of Cochran-Mantel-Haenszel test comparing caplacizumab with placebo, adjusting for GCS at randomization.

Source: Clinical Study Report for HERCULES.[10]

Health-Related Quality of Life

This outcome was not assessed in HERCULES.

Productivity

This outcome was not assessed in HERCULES.

Organ Damage Markers

The normalization of all three organ damage markers was one of the key secondary efficacy end points in HERCULES and ranked fourth in the statistical test hierarchy. For each of these outcomes, only patients with abnormal measurements at baseline were included in the analyses.

The Kaplan-Meier analysis of normalization of three organ damage markers (LDH, cardiac troponin, and serum creatinine) showed a trend toward faster normalization of these markers in patients treated with caplacizumab compared with those treated with placebo. The median time to normalization was 2.86 days (95% CI, 1.93 to 3.86) in the caplacizumab group and 3.36 days (95% CI, 1.88 to 7.71) in the placebo group, respectively. No formal statistical test was performed on this fourth key secondary end point, as the test on the third key secondary end point (proportion of patients with refractory aTTP) did not reach statistical significance.

Details of time to normalization of all three markers as well as time to normalization for each marker are presented in Table 11.

Table 11: Normalization of Organ Damage Markers (LDH, Cardiac Troponin, and Serum Creatinine) – ITT Population

	HERCULES	
	Caplacizumab (n = 72)	Placebo (n = 73)
All 3 markers		
Number of patients analyzed	65	66
Days, median (95% CI)	2.86 (1.93 to 3.86)	3.36 (1.88 to 7.71)
LDH		
Number of patients analyzed	[redacted]	[redacted]
Days, median (95% CI)	[redacted]	[redacted]
Cardiac troponin		
Number of patients analyzed	[redacted]	[redacted]
Days, median (95% CI)	[redacted]	[redacted]
Serum creatinine		
Number of patients analyzed	[redacted]	[redacted]
Days, median (95% CI)	[redacted]	[redacted]

CI = confidence interval; ITT = intention-to-treat; LDH = lactate dehydrogenase.

Note: For each of these outcomes, only patients with abnormal measurements at baseline were included in the analyses.

Source: Clinical Study Report for HERCULES.[10]

Prevention of Major Thromboembolic Events

This outcome was one component of a composite outcome (TTP-related death, recurrence of TTP, or at least one treatment-emergent major thromboembolic event). During the overall treatment period, which covered the double-blind daily PEX therapy and 30-day post–daily PEX therapy, the number of patients experiencing major thromboembolic events was similar between the caplacizumab group (six patients, 8.5%) and the placebo group (six patients, 8.2%).

Details of the prevention of major thromboembolic events are provided in Table 10 and Table 12.

Table 12: Prevention of Major Thromboembolic Events, ITT Population, Overall Study Period

	HERCULES	
	Caplacizumab (n = 72)	Placebo (n = 73)
Number of patients analyzed	71	73
Number of patients with ≥ 1 treatment-emergent major thromboembolic event, n (%)	6 (8.5)	6 (8.2)
Cerebrovascular accident	2 (2.8)	3 (4.1)
Myocardial infarction	1 (1.4)	1 (1.4)
Pulmonary embolism	1 (1.4)	0
Spontaneous DVT	0	1 (1.4)
Catheter-associated DVT	3 (4.2)	2 (2.7)

DVT = deep venous thrombosis; ITT = intention-to-treat.

Prevention of Refractory aTTP

Refractory aTTP was one of the key secondary efficacy end points in HERCULES and ranked third in the statistical test hierarchy. Refractory aTTP was defined as the absence of platelet count doubling after four days of standard treatment and an LDH greater than the ULN.

During the double-blind treatment period covering the daily PEX therapy period and the 30-day post–daily PEX therapy period, no patients in the caplacizumab group and three patients (4.2%) in the placebo group experienced refractory aTTP. The between-group difference in refractory aTTP was not statistically significant (P = 0.0572). When refractory aTTP was defined using the criteria developed by Scully et al., the between-group difference reached statistical significance (P = 0.0178).

Subgroup analyses based on severity of disease at baseline or previous TTP episodes was performed. However, the interpretation of results was challenging due to the small number of events in the treatment groups.

Details of prevention of refractory aTTP are provided in Table 13.

The sponsor provided an integrated efficacy analysis that included all randomized patients in HERCULES and TITAN.[23] The results showed that treatment with caplacizumab was associated with a statistically significant reduction in the number of patients who were refractory to therapy during the treatment period (zero patients in the caplacizumab groups compared with seven patients, 6.3% in the placebo groups). Details are provided in Appendix 3.

Table 13: Refractory aTTP – ITT Population, Double-Blind Study Treatment Period

	HERCULES	
	Caplacizumab (n = 72)	Placebo (n = 73)
Number of patients analyzed	71	73
Number of patients with refractory aTTP, n (%)[a]	0	3 (4.2)
P value	0.0572	
Subgroups (previous aTTP episode):		
Initial	[redacted]	[redacted]
Recurrent	[redacted]	[redacted]
Subgroups (baseline disease severity):		
Less severe	[redacted]	[redacted]
Very severe	[redacted]	[redacted]
Number of patients with refractory aTTP using Scully's criteria, n (%)[b]	[redacted]	[redacted]
P value	[redacted]	

aTTP = acquired thrombotic thrombocytopenic purpura; GCS = Glasgow Coma Scale; ITT = intention-to-treat; LDH = lactate dehydrogenase; TTP = thrombotic thrombocytopenic purpura; ULN = upper limit of normal.

Note: P value of Cochran-Mantel-Haenszel test comparing caplacizumab group with placebo, adjusted for GCS at randomization.

[a] Refractory TTP was defined as the lack of a doubling of the platelet count after four days of treatment (i.e., platelet count after four days of standard treatment divided by the count at start of treatment is < 2) and LDH > ULN.

[b] Refractory TTP was defined as a platelet count at day x below the platelet count at day x minus 1 for at least one value of x, where x = 2, 3, 4, or 5 and LDH > 1.5 × ULN from day 1 to day 5.

Source: Clinical Study Report for HERCULES.[10]

Time to Platelet Count Response

This was the primary efficacy end point in HERCULES. A statistically significantly shorter time to normalization of the platelet count was observed in the caplacizumab group (median 2.69 days; 95% CI, 1.89 to 2.83) compared with the placebo group (median 2.88 days; 95% CI, 2.68 to 3.56; P = 0.0099). A hazard ratio of 1.55 (95% CI, 1.095 to 2.195) generated with a Cox proportional hazards model indicated that, at any given time point, patients in the caplacizumab group were 1.55 times more likely to achieve a platelet count response compared with those in the placebo group (Table 14).

Results of the subgroup analyses based on GCS scores suggested that the time to normalization of the platelet count response was shorter in patients treated with caplacizumab compared with those treated with placebo.

Sensitivity analyses were performed to assess the robustness of the primary analysis result to different datasets, mITT population, and the per-protocol population. The results were very similar to those of the primary analysis (data not shown).

Table 14: Time to Platelet Count Response, ITT Population

	HERCULES	
	Caplacizumab (n = 72)	Placebo (n = 73)
Time to platelet count response, days		
25th percentile (95% CI)	1.75 (1.65 to 1.87)	1.94 (1.70 to 2.64)
Median (95% CI)	2.69 (1.89 to 2.83)	2.88 (2.68 to 3.56)
75th percentile (95% CI)	2.95 (2.85 to 3.81)	4.50 (3.78 to 7.79)
P value (stratified log-rank test)	0.0099	
HR (95% CI)	1.55 (1.095 to 2.195)	
Subgroup analysis		
GCS score ≤ 12		
Number of patients analyzed	6	5
Days, median (95% CI)	[redacted]	[redacted]
GCS score of 13 to 15		
Number of patients analyzed	65	67
Days, median (95% CI)	[redacted]	[redacted]

CI = confidence interval; GCS = Glasgow Coma Scale; HR = hazard ratio; ITT = intention-to-treat.

Note: Cox proportional hazards model with treatment group and GCS category as independent variables, a hazard ratio greater than 1 indicates advantage of caplacizumab.

Source: Clinical Study Report for HERCULES.[10]

Change in Platelet Counts From Baseline

At the end of the double-blind treatment period, more patients treated with caplacizumab ([redacted]) reached a platelet count of 150 × 10^9/L or higher compared with those in the placebo group ([redacted]) in the ITT population.

At the end of the open-label caplacizumab treatment period, [redacted] achieved a platelet count of 150 × 10^9/L or higher.

Neurological Assessment

The number of patients with neurological symptoms decreased from baseline during the daily PEX period and 30-day post–daily PEX period in both treatment groups. In patients

treated with caplacizumab, the proportion of patients with neurological symptoms decreased from [redacted] at the end of the follow-up period. In patients treated with placebo, the proportion of patients with neurological symptoms decreased from [redacted] at the end of the follow-up period.

Details of change in neurological symptoms are provided in Table 15.

Table 15: Neurological Symptoms, ITT Population

	HERCULES	
	Caplacizumab (n = 72)	Placebo (n = 73)
Neurological symptoms		
Baseline, n (%)	[redacted]	[redacted]
End of daily PEX period, n (%)	[redacted]	[redacted]
End of 30-day post–daily PEX period, n (%)	[redacted]	[redacted]
End of follow-up period, n (%)	[redacted]	[redacted]

ITT = intention-to-treat; PEX = plasma exchange.

Source: Clinical Study Report for HERCULES.[10]

Cognitive Assessment

The median SMMSE scores at baseline were [redacted] in the caplacizumab group and [redacted] in the placebo group. The scores were considered within the normal range using the general population as a reference.[21] During the treatment period, SMMSE scores increased (improved) in both treatment groups on day 5 of daily PEX as well as at the end of the 30-day post–daily PEX period. The improvement was maintained at the end of the follow-up period in both groups.

Cognitive assessment details are presented in Table 16.

Table 16: Cognitive Assessment, ITT Population

	HERCULES	
	Caplacizumab (n = 72)	Placebo (n = 73)
SMMSE score		
Baseline, median (range)	[redacted]	[redacted]
Number of patients analyzed	[redacted]	[redacted]
Day 5 of daily PEX period, median (range)	[redacted]	[redacted]
Number of patients analyzed	[redacted]	[redacted]
End of 30-day post–daily PEX period, median (range)	[redacted]	[redacted]
Number of patients analyzed	[redacted]	[redacted]
End of follow-up period, median (range)	[redacted]	[redacted]

ITT = intention-to-treat; PEX = plasma exchange; SMMSE = Standardized Mini-Mental State Examination.

Source: Clinical Study Report for HERCULES.[10]

Hospitalization Due to aTTP Episodes

Treatment with caplacizumab was associated with a reduction in the number of days in the ICU and hospital during the overall treatment period compared with placebo. The overall treatment period included data from the post–daily PEX period and the open-label treatment period (where patients were analyzed according to their initial treatment allocation).

During the daily PEX period, the mean number of days in ICU was [redacted] in the caplacizumab group and [redacted] in the placebo group. During the overall treatment period, including the open-label caplacizumab period, the mean number of days in ICU was 3.4 days in the caplacizumab group and 9.7 days in the placebo group. During the overall treatment period, including the follow-up period, the mean number of days in ICU was [redacted] in the caplacizumab group and [redacted] in the placebo group.

During the daily PEX period, the mean number of days in hospital was [redacted] in the caplacizumab group and [redacted] in the placebo group. During the overall treatment period, including the open-label caplacizumab period, the mean number of days in hospital was 9.9 days in the caplacizumab group and 14.4 days in the placebo group. During the overall treatment period, including the follow-up period, the mean number of days in hospital was [redacted] in the caplacizumab group and [redacted] in the placebo group.

Details related to duration of ICU stay or hospital stay are presented in Table 17.

Table 17: Days in ICU and Hospital, ITT Population

	HERCULES	
	Caplacizumab (n = 72)	Placebo (n = 73)
Number of days in ICU		
Daily PEX period		
Number of patients analyzed	[redacted]	[redacted]
Number of days, mean (SE)	[redacted]	[redacted]
Number of days, median (range)	[redacted]	[redacted]
Overall treatment period, including OL period		
Number of patients analyzed	28	27
Number of days, mean (SE)	3.4 (0.40)	9.7 (2.12)
Number of days, median (range)	3.0 (1 to 10)	5.0 (1 to 47)
Overall treatment period including follow-up period		
Number of patients analyzed	[redacted]	[redacted]
Number of days, mean (SE)	[redacted]	[redacted]
Number of days, median (range)	[redacted]	[redacted]
Number of days in hospital		
Daily PEX period		
Number of patients analyzed	[redacted]	[redacted]
Number of days, mean (SE)	[redacted]	[redacted]
Number of days, median (range)	[redacted]	[redacted]
Overall treatment period, including OL period		
Number of patients analyzed	71	73
Number of days, mean (SE)	9.9 (0.70)	14.4 (1.22)
Number of days, median (range)	9.0 (2 to 37)	12.0 (4 to 53)
Overall treatment period, including follow-up period		
Number of patients analyzed	[redacted]	[redacted]
Number of days, mean (SE)	[redacted]	[redacted]
Number of days, median (range)	[redacted]	[redacted]

ICU = intensive care unit; ITT = intention-to-treat; OL = open-label; PEX = plasma exchange; SE = standard error.

Source: Clinical Study Report for HERCULES.[10]

Harms

Only those harms identified in the review protocol are reported subsequently. See Table 18 for detailed harms data.

Adverse Events

During the overall study period, almost all patients reported AEs in HERCULES: 97.2% in the caplacizumab group and 97.3% in the placebo group. [redacted]. AEs were reported in 89.3% of patients during the open-label caplacizumab therapy period.

During the overall study period, the most common AEs reported in the caplacizumab group were epistaxis (32.4%), headache (22.5%), gingival bleeding (18.3%), urticaria (16.9%), pyrexia (14.1%), fatigue (14.1%), nausea (14.1%), and TTP episodes (12.7%). In the placebo group, TTP episodes (39.7%), rash (12.3%), and contusion (13.7%) were commonly reported. In the open-label caplacizumab therapy period, catheter-site hemorrhage (28.6%), epistaxis (17.9%), gingival bleeding (14.3%), and gastrointestinal symptoms (14.3%) were commonly reported.

Serious Adverse Events

SAEs were reported for 28 patients (39.4%) in the caplacizumab group and 39 patients (53.4%) in the placebo group during the overall study period. The majority of the SAEs reported in the placebo group occurred during the post–daily PEX period (46.9%). During the open-label caplacizumab therapy, seven patients (25%) reported SAEs. TTP episodes were the most commonly reported SAEs, and the incidence of TTP episodes was higher in the placebo group (39.7%) than in the caplacizumab group (12.7%).

Withdrawals Due to Adverse Events

During the overall study period, five patients (7.0%) treated with caplacizumab and nine patients (12.3%) treated with placebo withdrew from the study or treatment due to AEs. During the open-label caplacizumab therapy period, one patient withdrew due to AEs.

Mortality

Three patients in the placebo group died during the daily PEX treatment period. All deaths were considered to be TTP-related by the independent adjudication committee. One patient in the caplacizumab group died in the follow-up period. See Survival (page 44) for more details.

Notable Harms

During the overall study period, the risk of bleeding events was similar between treatment groups: 49 patients (69%) in the caplacizumab group and 49 patients (67.1%) in the placebo group. Hypersensitivity was experienced by [redacted] in the caplacizumab group and [redacted] in the placebo group. Anti-drug antibodies were found in two patients (2.8%) in the caplacizumab group and one patient (1.4%) in the placebo group.

During the open-label treatment with caplacizumab, [redacted], and anti-drug antibodies were detected in one patient (3.8%).

Table 18: Summary of Harms, Safety Population

	Overall study period[a]		Open-label period[b]
	Caplacizumab (N = 71)	Placebo (N = 73)	Caplacizumab (N = 28)
Patients with ≥ 1 AE			
n (%)	69 (97.2)	71 (97.3)	25 (89.3)
Most common events[c]			
Fatigue	10 (14.1)	6 (8.2)	2 (7.1)
Catheter-site hemorrhage	5 (7.0)	5 (6.8)	8 (28.6)
Pyrexia	10 (14.1)	6 (8.2)	1 (3.6)
Nausea	10 (14.1)	7 (9.6)	2 (7.1)
Gingival bleeding	13 (18.3)	1 (1.4)	4 (14.3)
Constipation	7 (9.9)	5 (6.8)	4 (14.3)
Diarrhea	7 (9.9)	5 (6.8)	4 (14.3)
Abdominal pain upper	NR	NR	4 (14.3)
Headache	16 (22.5)	6 (8.2)	6 (21.4)
Paresthesia	8 (11.3)	6 (8.2)	0
Epistaxis	23 (32.4)	2 (2.7)	5 (17.9)
Urticaria	12 (16.9)	5 (6.8)	1 (3.6)
Rash	5 (7.0)	9 (12.3)	4 (14.3)
TTP	9 (12.7)	29 (39.7)	4 (14.3)
Anemia	4 (5.6)	6 (8.2)	4 (14.3)
Contusion	5 (7.0)	10 (13.7)	2 (7.1)
Patients with ≥ 1 SAE			
n (%)	28 (39.4) [redacted]	39 (53.4) [redacted]	7 (25.0)
Most common events (frequency > 2%)	TTP (12.7%), epistaxis (5.6%), headache (2.8%)	TTP (39.7%)	TTP (14.3%), upper GI hemorrhage (3.6%), dyspnea (3.6%), seizure (3.6%), rash erythematous (3.6%)
WDAEs			
n (%)	5 (7.0)	9 (12.3)	1 (3.6)
Most common events	MI (1), ventricular fibrillation (1), upper GI hemorrhage (1), epistaxis (1), TTP (1)	MI (1), hypoxia (1), TTP (2), DVT (1), jugular vein thrombosis (1), anaphylactic transfusion reaction (1), GGT elevated (1)	TTP (1)
Deaths			
n	1 (follow-up period)	3 (daily PEX period)	0

	Overall study period[a]		Open-label period[b]
	Caplacizumab (N = 71)	Placebo (N = 73)	Caplacizumab (N = 28)
At least 1 TEAE leading to death, n (%)	1 (1.4)	3 (4.1)	0
Notable harms			
Bleeding event, n (%)	49 (69.0)	49 (67.1)	22 (78.6)
Hypersensitivity, n (%)	[redacted]	[redacted]	[redacted]
ADA positive, n (%)	2 (2.8)	1 (1.4)	1 (3.8)

ADA = anti-drug antibody; AE = adverse event; DVT = deep vein thrombosis; GGT = gamma-glutamyl transferase; GI = gastrointestinal; MI = myocardial infarction; NR = not reported; PEX = plasma exchange; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TTP = thromboembolic thrombocytopenic purpura; WDAE = withdrawal due to adverse event.

[a] Events started in the double-blind or follow-up period for patients with no open-label period.

[b] Events started in the open-label or follow-up period.

[c] Frequency > 10%.

Source: Clinical Study Report for HERCULES.[10]

Critical Appraisal

Internal Validity

In HERCULES, appropriate methods were used to randomize patients to treatments and conceal treatment allocation. In general, the patient characteristics appear to be balanced at baseline between groups, although some imbalance was observed. Compared with the placebo group, patients in the caplacizumab group had fewer previous TTP episodes, were characterized as having more severe conditions, had fewer patients with ADAMTS13 levels less than 10%, and had higher cTnI levels and higher LDH levels at baseline. In HERCULES, patient's baseline disease severity was defined using a French severity score in which brain involvement, LDH, age, neurological involvement, and cardiac involvement were taken into account; however, the clinical experts consulted for this review indicated that, in clinical practice, it is difficult to define disease severity, and the scale used in the trial is not used in practice settings. Although imbalances in baseline characteristics occur in RCTs of treatments for rare diseases, despite randomization, the imbalance in baseline characteristics may have an impact on data interpretation and could bias the results. For example, more patients in the placebo group had previous aTTP episodes before entering the study. Consequently, a diagnosis of aTTP could be quickly established and appropriate treatment could be delivered without delay. Early diagnosis and prompt treatment are associated with faster recovery and fewer complications in the target population.[2,8] Therefore, this may bias the results toward the placebo group. However, it is otherwise uncertain to what extent the imbalances in the other baseline characteristics would influence the relative treatment effect between caplacizumab and placebo.

In HERCULES, 2.8% of patients in the caplacizumab group and 35.6% of patients in the placebo group were switched to open-label caplacizumab. When analyzing data in the open-label caplacizumab population (defined as "all patients who received at least one administration of open-label caplacizumab," regardless which initial treatment patient received), only data collected after the switch to open-label caplacizumab were used. Due to the notably different proportions of patients switched from the two initially assigned treatment groups, the results related to deaths, normalization of organ dysfunction, neurological involvement, or the risk of major thrombotic events could have been biased, and a reduced effect size of clinical benefits from caplacizumab could have been observed.

In addition, the two treatment groups differed in their use of rituximab during the overall study period (40.0% in the caplacizumab group versus 49.3% in the placebo group) or the double-blind daily PEX period (17.1% in the caplacizumab group versus 29.6% in the placebo group), with higher use in the placebo arm in HERCULES. This could also have an impact on the treatment effect of caplacizumab when compared with placebo. Since rituximab alters the disease course, the efficacy and safety outcomes may be biased against caplacizumab.

Standard of care for aTTP included PEX and corticosteroids, with or without rituximab. The treatment protocols are not standardized in different countries or regions in terms of intensity and frequency of the treatment. Since all patients were randomized to receive the study drug, there is no clear evidence that the diversity in the standard-of-care regimen biased the study findings.

Attrition bias occurred when more placebo-treated patients discontinued the study compared with caplacizumab-treated patients. The main reason for early discontinuation was AEs, withdrawal of consent, and physician's decision. It is unclear whether "withdrew consent" and "physician's decision" are related to lack of treatment effect, AEs, or other reasons. The ITT approach used in the data analyses may not be able to adequately handle this bias, as no imputation of missing data was conducted for many of the outcomes in HERCULES.

Treatment effects of the study drug were assessed in various periods, such as the double-blind daily PEX therapy period, 30-day post–daily PEX period, extension treatment period, and open-label caplacizumab therapy period. Some patients who were initially assigned to the placebo group had to switch to caplacizumab therapy due to disease recurrence. This would complicate the data analysis and result interpretation for some of the efficacy outcomes, especially for long-term outcomes, for example, the risk of recurrence of aTTP in the future or days on PEX. In the analysis of the composite end point of TTP-related death, recurrence of aTTP, and occurrence of major thromboembolic events, switching to open-label caplacizumab therapy was not an issue for data analysis, as only events that had occurred prior to a switch to open-label caplacizumab were evaluated. For time to platelet count response, the primary efficacy outcome in HERCULES, the switching of patients who experienced a recurrence of aTTP during the study to open-label caplacizumab did not affect the primary efficacy analysis, as a recurrence can occur only after platelet count response, according to the definition of this outcome (initial platelet count ≥ 150 × 10^9/L with the subsequent stopping of daily PEX within five days).

In terms of the methods of statistical analysis, a hierarchical testing procedure was used to account for multiple comparisons among the primary end point and key secondary end points. The hierarchical sequence in the included studies was pre-specified and included clinically relevant outcomes that are commonly accepted in thrombocytopenic disorders. Outcomes outside of the testing hierarchy, such as occurrence of certain major cardiovascular events such as myocardial infarction or stroke, need to be interpreted with caution due to the possible inflated type I error. In HERCULES, efficacy outcomes, except for the primary and key secondary outcomes (e.g., neurological and cognitive assessments, and hospital and ICU stays), were descriptively summarized using the number of observations, means, and SE. Formal statistical tests were not performed for these outcomes.

The study indicated that efficacy analyses were performed in an ITT population. However, a violation of ITT principles was observed in the analyses of several efficacy outcomes. For

example, for the outcome of refractory aTTP, patients who were discontinued because they were lost to follow-up or withdrew consent before day 5 were excluded from the analysis. In addition, the proportion of missing data was substantial (> 20%), as was the differential between caplacizumab and placebo for the outcomes of time to normalization of organ damage markers and cognitive assessments. Therefore, bias may have been introduced into the results. For the outcomes of platelet count response or days on PEX therapy, the impact of missing data on the study results would be minimal because all patients tended to complete the treatment with PEX. Missing data were not imputed for most of the outcome measures, and no effort was made to account for the missing patient(s), except for the outcome of refractory aTTP, where a multiple imputation approach was adopted. The HERCULES Clinical Study Report stated that all efficacy analyses were conducted on the ITT population; however, according to the data provided, many of the results were assessed in a subset of the sample, thus indicating that an mITT population could have been used. Note that the ITT population included 145 patients, while the mITT population included 144 patients.

In HERCULES, the mortality rate in the placebo group, where patients received standard of care, was much lower than what would be expected in clinical practice settings (may range from 10% to 20%). The nature of a clinical trial setting and the relatively shorter duration of HERCULES likely explains part of this discrepancy, although the fact that the placebo group may not represent the true baseline risk of aTTP-related events should be considered when interpreting the data.

Predefined subgroup analyses based on various baseline patient characteristics were conducted to examine the consistency of the primary analysis results across subgroup levels. A stratification variable at randomization was included. Thus, the balance of patient baseline characteristics was likely to be maintained between subgroups. However, due to the small number of patients in some of the subgroups, results should be interpreted with caution.

Health-related quality of life is an important clinical outcome for patients with aTTP; however, this was not measured in HERCULES.

External Validity

According to the clinical experts involved in the review, the inclusion and exclusion criteria for the study are reasonable and generally consistent with clinical practice.

According to the clinical panel of this review, misdiagnosis is common for aTTP, as other conditions (e.g., thrombocytopenia or red cell fragments on the blood smear from other causes) may mimic aTTP. Patients may be given inappropriate treatment that, consequently, could have an impact on improvement in health outcomes. For example, patients with disseminated malignancy who present with MAHA and thrombocytopenia may receive PEX treatment and experience AEs related to PEX, but could delay the appropriate cancer treatments.[24] Therefore, there is a concern for the generalizability of the study results to patients who actually have aTTP. Furthermore, severe ADAMTS13 deficiency (activity < 10%) typically confirms the diagnosis of aTTP. However, activity less than 10% is not 100% sensitive or specific for aTTP. For example, patients with sepsis or systemic cancer may have an ADAMTS13 activity level less than 10%, while aTTP patients who have received multiple transfusions of PEX containing functional ADAMTS13 may have an ADAMTS13 activity of 10% to 20%.[1] In HERCULES, 10% to 18% of study participants had ADAMTS13 levels of 10% or higher. All study participants received one PEX before

randomization; this may have increased their ADAMTS13 levels at baseline. Four patients (5.6%) in the caplacizumab group and three (4.1%) in the placebo group who were initially diagnosed with aTTP had an alternative diagnosis later in the trial.[11] The misdiagnosis rate was low and is less likely to have a significant impact on the generalizability of the study results.

According to the clinical experts consulted for this review, the use of rituximab is lower in Canada than what was observed in HERCULES, where the proportion of patients who received rituximab during the overall study period was 40% to 50%. Rituximab use is lower in practice because the drug must be obtained through special access mechanisms, as it does not have Health Canada approval for use in aTTP and is not reimbursed by drug plans for this indication.

Due to the relatively short duration (two to six months) of the included study, some important clinical outcomes could not be sufficiently examined, such as survival, TTP relapses, and safety in the long run.

Indirect Evidence

No indirect comparison analysis was submitted for this review.

Other Relevant Studies

Other Relevant Studies: Phase II RCT

Methods

The TITAN study was a phase II, multi-centre, single-blind, parallel design, placebo-controlled RCT conducted in adult patients who were symptomatic and experiencing acute episodes of aTTP that required treatment with PEX. Only the patients were blinded to the treatment at the time of randomization.

Populations

To be eligible for the TITAN study, patients needed to be at least 18 years of age with a clinical diagnosis of aTTP and in need of PEX (at least one session prior to randomization). Patients were excluded from the study if they had a platelet count of 100,000/µL or higher, severe active infection indicated by sepsis, evidence of infection with E. coli 0157, antiphospholipid syndrome, diagnosis of disseminated intravascular coagulation, transplantation-associated thrombotic microangiopathy, congenital TTP, a high risk of or active bleeding, uncontrolled arterial hypertension, or were receiving chronic treatment with anticoagulant therapy that could not be stopped safely.

The treatment groups were balanced by baseline characteristics, except for gender, as 51.4% and 31.4% of patients were male in the placebo and caplacizumab groups, respectively (Table 19).

Table 19: Baseline Characteristics (Safety Population)

	Caplacizumab (N = 35)	Placebo (N = 37)
Age (years), mean (SD)	41.2 (12.43)	43.1 (13.26)
Age (years), minimum, maximum	19, 72	21, 67
Gender, n (%)		
Male	11 (31.4)	19 (51.4)
Female	24 (68.6)	18 (48.6)
Race		
White	31 (88.6)	33 (89.2)
Black	4 (11.4)	4 (10.8)

SD = standard deviation.

Source: TITAN Clinical Study Report;[25] Peyvandi et al. (2016).[26]

The baseline disease characteristics by treatment group are summarized in Table 20. The two groups differed in the mean (SD) number of days for PEX before enrolment, with the placebo group reporting more days than the caplacizumab group (mean [SD] of [redacted]. Also, a greater proportion of patients in the placebo group had an ADAMTS13 activity level of 10% or higher (15.4% compared with 5.6%).

Table 20: Baseline Disease Characteristics (ITT Population)

	Caplacizumab (N = 36)	Placebo (N = 39)
Baseline platelet count (10^3/mm^3), mean (SD)	21.1 (18.15)	28.0 (19.97)
Previous aTTP episodes, n (%)		
Initial	24 (66.7)	27 (69.2)
Recurrent	12 (33.3)	12 (30.8)
Number of days for PEX before enrolment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]
ADAMTS13 activity,[a] n (%)		
< 10%	28 (77.8)	30 (76.9)
≥ 10%	2 (5.6)	6 (15.4)
Missing	6 (16.7)	3 (7.7)
TnI (ng/mL), mean (SD)	[redacted]	[redacted]
LDH (U/L), mean (SD)	1,277.37 (852.503)	1,270.09 (939.336)
vWF:Ag (%), mean (SD)	180.26 (78.176)	189.60 (74.265)
PEX prior to randomization, n (%)	2 (5.6)	4 (10.3)

ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ITT = intention-to-treat; LDH = lactate dehydrogenase; PEX = plasma exchange; SD = standard deviation; TnI = troponin I; TTP = thrombotic thrombocytopenic purpura; U/L = units per litre; vWF:Ag = von Willebrand factor antigen.

[a] Post hoc analysis.

Source: TITAN Clinical Study Report;[25] Peyvandi et al. (2016).[26]

Interventions

Patients were randomized 1:1 to receive either caplacizumab or placebo, administered daily in addition to standard-of-care treatment with PEX that was also provided daily. The interventions were taken for the duration of the PEX treatment period, followed by an additional 30 days following treatment.

More specifically, caplacizumab (10 mg) or placebo was administered as an IV bolus before PEX was initiated on-study, and again subcutaneously within 30 minutes following the first PEX. After the first PEX, daily subcutaneous caplacizumab (10 mg) or placebo was administered following the PEX procedure, and then once daily for the 30 days after the last PEX.

Standard of care included daily PEX, with decisions to discontinue or reduce (taper) treatment made at the discretion of the investigator. Additionally, one or more of the following treatments may also be included: adjunctive immunosuppressive treatment with corticosteroids or rituximab, antiplatelet drugs such as Aspirin, supportive therapy with red cell transfusion or folate supplementation, and treatment with vincristine or cyclosporin in the case of refractory TTP. Low molecular weight heparin could also be used in patients at high risk of venous thromboembolism.

Outcomes

The primary efficacy analysis was time to response. Response was defined by the recovery of platelets (≥ 150,000/μL) and a confirmed platelet response (platelet count at 48 hours following the initial reporting of platelet count recovery and an LDH that was twice the ULN or less).

Secondary efficacy analyses that met the protocol outlined for this review included complete remission, exacerbations of TTP and TTP relapse, PEX, mortality, a platelet count of 150,000/μL or higher, resolution or improvement of TTP-related signs and symptoms, and incidence of PEX-related AEs. Additionally, the GCS score and neurocognitive battery were reported by the sponsor, as well.

Safety outcomes were also included in this review.

Statistical Analysis

The study was statistically powered for the primary end point and no adjustments were made for multiplicity for the secondary variables. The efficacy analyses were performed using the ITT population and missing data were not imputed for any of the outcomes unless otherwise specified. Any P values reported for secondary outcomes were exploratory.

The primary efficacy analysis censored observations that did not meet a defined time interval of 30 days after the first administration of the study drug due to a patient being lost to follow-up (for any reason) or an end point not being reached.

Patient Disposition

The patient disposition for the TITAN study has been summarized in Table 21. Of the 76 patients screened, 75 were randomized to either caplacizumab (n = 36) or placebo (n = 39). Approximately half of the patients in both treatment groups completed the study (55.6% and 53.8% for caplacizumab and placebo, respectively). In other words, the discontinuation rate

was between 44.4% for caplacizumab and 46.2% for placebo. The most common reason for discontinuing the study was that the study was terminated by the sponsor.

Table 21: Patient Disposition

	Caplacizumab	Placebo
Screened	76	
Randomized	36	39
Completed study	20 (55.6)	21 (53.8)
Discontinued study	16 (44.4)	18 (46.2)
AE or drug reaction	3 (8.3)	0
Withdrawal of consent	1 (2.8)	3 (7.7)
Lost to follow-up	1 (2.8)	0
Physician decision	1 (2.8)	1 (2.6)
Protocol violation	0	1 (2.6)
Study terminated by sponsor	9 (25.0)	10 (25.6)
Pregnancy	0	1 (2.6)
Death	0	1 (2.6)
Other	1 (2.8)	1 (2.6)
ITT, N	36	39
PP, N	10	15
Safety, N	35	37

AE = adverse event; ITT = intention-to-treat; PP = per-protocol.

Source: TITAN Clinical Study Report.[25]

Exposure to Study Treatments

The duration of exposure to the study drug was similar between groups both overall and during the phase following daily PEX (Table 22). Of note, during the PEX phase, the placebo group was exposed to the study drug for a mean (SD) number of days of [redacted], compared with the caplacizumab group, which was exposed for a mean (SD) of [redacted]. The use of rituximab during PEX differed between the two treatment groups as well, with 23.1% and 5.6% of patients in the placebo and caplacizumab groups, respectively, reporting the use of rituximab (Table 23).

Table 22: Extent of Exposure (Safety Population)

	Caplacizumab (N = 35)	Placebo (N = 37)
Duration of exposure to study drug (days)		
Mean (SD)	37.9 (14.99)	39.2 (18.61)
Minimum, maximum	3, 77	2, 90
Duration of exposure to study drug during PEX phase (days)		
Mean (SD)	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]
Duration of exposure to study drug after daily PEX phase (days)		
Mean (SD)	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]

PEX = plasma exchange; SD = standard deviation.

Source: TITAN Clinical Study Report.[25]

Table 23: Concomitant Medication During PEX (ITT Population)

	Caplacizumab (N = 35)	Placebo (N = 37)
Proportion of patients with corticosteroid use during PEX, n (%)	32 (88.9)	36 (92.3)
Proportion of patients with rituximab use during PEX, n (%)	2 (5.6)	9 (23.1)

ITT = intention-to-treat; PEX = plasma exchange.

Source: TITAN Clinical Study Report;[25] Peyvandi et al. (2016).[26]

Efficacy

Survival

No deaths were reported during the daily PEX period or within the study treatment period. During the time from the end of study treatment up to and including the one-month follow-up, two (5.1%) deaths were reported, both from the placebo group.

Reduction in the Use of PEX

During the initial PEX period, patients randomized to caplacizumab received a mean of 6.7 (SD = 3.69) daily PEX sessions compared with 8.4 (SD = 6.74) for patients randomized to placebo (Table 24). The range for the number of daily PEX sessions was from [redacted]. The other PEX-related efficacy outcomes presented in Table 24 were similar between treatment groups; however, the ranges corresponding to PEX administration outcomes (i.e., the number of consecutive days of PEX and number of days with one or more PEX administrations) was wider for the placebo group.

Table 24: PEX-Related Efficacy Outcomes (ITT Population)

	Caplacizumab N = 36	Placebo N = 39
During the initial PEX period		
Number of daily PEX sessions		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]
Total volume of PEX administered (mL)		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]
Number of consecutive days of PEX administration		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]
During the total course of the study		
Number of days with ≥ 1 PEX administration		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]
Proportion of patients with PEX tapering		
n (%)	11 (30.6)	11 (28.2)
P value	0.975[a]	

ITT = intention-to-treat; PEX = plasma exchange; SD = standard deviation.

[a] Outcome was outside the statistical testing hierarchy.

Source: TITAN Clinical Study Report;[25] Peyvandi et al. (2016).[26]

aTTP Relapses and Exacerbations

During the entire study period, including up to 12 months of follow-up, 11 patients (30.6%) in the caplacizumab treatment group experienced a relapse of TTP compared with three patients (7.7%) in the placebo group (Table 25). The time to first relapse of TTP in the 11 patients treated with caplacizumab was [redacted]. Of note, all but one of the 11 patients had their first relapse [redacted]. For the three patients who relapsed in the placebo group, [redacted].

The proportion of patients with exacerbations within 30 days following the last day of initial daily PEX was also reported. For the caplacizumab group, 8.3% (95% CI, 1.8 to 22.5) of patients experienced an exacerbation, compared with 28.2% (95% CI, 15.0 to 44.9) of patients in the placebo group.

Response to Treatment (Confirmed Platelet Response and Remission)

The primary outcome for the TITAN study was the time to response, defined by confirmed normalization of platelet counts. A confirmed platelet response was reported for 86.1% patients treated with caplacizumab and 71.8% of the placebo group, which corresponded to a statistically significant (P = 0.005) hazard ratio of 2.20 (95% CI, 1.28 to 3.78). [redacted]

[redacted].

The proportion of patients with complete remission following initial daily PEX was 80.6% (95% CI, 64.0 to 91.8) for caplacizumab and 46.2% (95% CI, 30.1 to 62.8) for placebo (Table 25).

Table 25: Platelet Response, Remission, Relapse, and Exacerbations (ITT Population)

	Caplacizumab N = 36	Placebo N = 39
Primary efficacy outcome		
Confirmed platelet response[a]		
Patients censored at 30 days, n (%)	5 (13.9)	11 (28.2)
n (%)	31 (86.1)	28 (71.8)
HR (95% CI)	2.20 (1.28 to 3.78)[b]	
P value	0.005	
Secondary efficacy outcomes		
Patients with complete remission following initial daily PEX, n	29	18
Proportion of patients (95% CI)	80.6 (64.0 to 91.8)	46.2 (30.1 to 62.8)
Patients with exacerbations within 30 days of last day of initial daily PEX, n	3	11
Proportion of patients (95% CI)	8.3 (1.8 to 22.5)	28.2 (15.0 to 44.9)
Patients with relapse of TTP (occurred later than 30 days after last daily PEX), n	11	3
Proportion of patients (95% CI)	30.6 (16.3 to 48.1)	7.7 (1.6 to 20.9)

CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; LDH = lactate dehydrogenase; PEX = plasma exchange; TTP = thrombotic thrombocytopenic purpura.

[a] Response is defined as a recovery of platelets of 150,000/μL or higher (confirmed 48 hours after the initial reporting by a de novo measure of platelets at that level or higher) and an LDH ≤ 2 × ULN.

[b] The hazard ratio is on a stratified Cox proportional hazards regression model with one PEX session prior to randomization (yes, no) as a covariate.

Source: TITAN Clinical Study Report;[25] Peyvandi et al. (2016).[26]

Change in Platelet Counts From Baseline

Lastly, based on the ITT population, 33 (91.7%) and 30 (76.9%) patients in the caplacizumab and placebo groups, respectively, had a platelet count of 150,000/μL or higher at the last administration of study treatment (day 30). At the one-month follow-up, 29 patients (80.6%) receiving caplacizumab had a platelet count of 150,000/μL or higher as well as 30 patients (76.9%) in the placebo group.

Harms

A summary of the harms reported for the TITAN study has been provided in Table 26. Almost every patient in the TITAN study reported at least one TEAE. The most common AEs reported in the caplacizumab and placebo groups, respectively, were TTP ([redacted]), headache (34.3% and 27.0%), epistaxis (31.3% and 10.8%), and nausea (28.6% and 29.7%). About half of patients in both treatment groups reported at least one serious AE (57.1% for caplacizumab and 51.4% for placebo). Of note, the most common serious AE was TTP ([redacted] for caplacizumab and placebo, respectively). Epistaxis, dizziness, and serious TTP events were reported more frequently in the caplacizumab-

treated group than placebo. Anemia, arthralgia, and asthenia were more common in the placebo group than the caplacizumab group.

Withdrawals due to AEs, deaths, and notable harms are also reported in Table 26. Four patients receiving caplacizumab withdrew from the study due to an AE, as did two patients receiving placebo. In addition, two deaths were reported, both from the placebo group and related to TTP. Regarding the notable harms, 54.3% and 37.8% of patients receiving caplacizumab and placebo, respectively, reported a bleeding event. [redacted] and three patients (9%) in the caplacizumab treatment group reported anti-drug antibodies.

Table 26: Summary of Harms (Safety Population)

	Caplacizumab N = 35	Placebo N = 37
Patients with ≥ 1 adverse event		
n (%)	34 (97.1)	37 (100)
Most common events,[a] n (%)		
TTP	13 (37.1)	14 (37.8)
Headache	12 (34.3)	10 (27.0)
Epistaxis	11 (31.3)	4 (10.8)
Nausea	10 (28.6)	11 (29.7)
Paresthesia	8 (22.9)	8 (21.6)
Dizziness	8 (22.9)	3 (8.1)
Vomiting	7 (20.0)	8 (21.6)
Constipation	7 (20.0)	10 (27.0)
Myalgia	7 (20.0)	1 (2.7)
Diarrhea	6 (17.1)	3 (8.1)
Fatigue	6 (17.1)	5 (13.5)
Pyrexia	6 (17.1)	6 (16.2)
Pain in extremity	5 (14.3)	8 (21.6)
Hypertension	5 (14.3)	6 (16.2)
Anemia	3 (8.6)	8 (21.6)
Arthralgia	3 (8.6)	8 (21.6)
Asthenia	1 (2.9)	6 (16.2)
Patients with ≥ 1 SAE		
n (%)	20 (57.1)	19 (51.4)
Most common events,[b] n (%)		
TTP	11 (31.4)	5 (13.5)
Anemia	2 (5.7)	0
Platelet count decreased	2 (5.7)	1 (2.7)
Patients with ≥ WDAE		
n (%)	4 (11.4)	2 (5.4)
[redacted]	[redacted]	[redacted]

	Caplacizumab N = 35	Placebo N = 37
Deaths		
n (%)	0	2
		Refractory TTP (1); cerebral hemorrhage related to TTP (1)
Notable harms, n (%)		
Bleeding event,[c] n (%)	19 (54.3)	14 (37.8)
Hypersensitivity, n (%)	[redacted]	[redacted]
ADA positive, n (%)	3 (9)	0

ADA = anti-drug antibody; SAE = serious adverse event; TTP = thrombotic thrombocytopenic purpura; WDAE = withdrawal due to adverse event.

[a] Frequency ≥ 15%.

[b] Frequency ≥ 5%.

[c] A bleeding event was defined as moderate-to-severe (including life-threatening) bleeding requiring urgent medical and/or surgical intervention.

Source: TITAN Clinical Study Report;[25] Peyvandi et al.[26]

Critical Appraisal

Internal Validity

The TITAN study was a single-blind, phase II, placebo-controlled RCT. Investigators were informed of the treatments assigned upon randomization. Knowledge of treatment assignment may have biased the reporting of safety-related data and also may have impacted treatment decisions for patients. The lack of blinding creates considerable uncertainty in the reporting of safety and efficacy data in this study. There are some differences to note between the two treatment groups in terms of baseline characteristics, including gender, number of days for PEX before enrolment, the proportion of patients with an ADAMTS13 activity level of 10% or higher, and the proportion of patients treated with PEX prior to randomization, which may have an impact on the observed efficacy and safety outcomes. As discussed in the critical appraisal of the pivotal trial (HERCULES), the primary efficacy analysis was related to platelet counts, which may be an inappropriate measure of efficacy because it is related to the mechanism of action of the drug and not the ability of the drug to treat the disease. Further analyses of efficacy conducted in the TITAN study are limited by a lack of adjustment for multiplicity and statistical testing. In addition, the study was powered only for the primary end point. Also of note, the two treatment groups differed in their use of rituximab during PEX, with higher use in the placebo arm. Since rituximab alters the disease course, the efficacy and safety outcomes may be biased against caplacizumab; however, the use of concomitant medications among the treatment arms is fair, considering the acute and severe nature of the disease. Lastly, follow-up assessments were conducted up to one month following study treatment. Similar to the design of the HERCULES trial, the duration of follow-up may have been too short to adequately capture the harms related to treatment with caplacizumab.

External Validity

The generalizability of this study is compromised by a lack of study centres within Canada. As described in both the clinician and patient input, the standard of care for aTTP is variable, even within Canada. Consequently, the lack of centres in Canada limits the applicability of the results to the Canadian context. Further, the demographics of the population included in this study may not reflect the diversity of patients within Canada. Regarding the severity of disease, the levels of LDH and troponin I were high but typical of patients with TTP.

Summary

Briefly, the efficacy of caplacizumab compared with placebo was demonstrated based on confirmed platelet response, which was the primary outcome in the TITAN study. Patients treated with caplacizumab were more likely to reach a confirmed platelet response compared with those treated with placebo based on a hazard ratio of 2.20 (95% CI, 1.28 to 3.78) that was statistically significant (P = 0.005). In terms of safety, almost every patient experienced at least one AE, and more than half of all patients experienced at least one SAE. The most common AE and SAE was TTP. The most common AEs following TTP in the caplacizumab group were headache, epistaxis, and nausea. Of note, reports of serious TTP and bleeding events were more common among patients treated with caplacizumab compared with placebo. Overall, the TITAN study demonstrated efficacy and highlighted safety signals that should be considered with the use of caplacizumab; however, the interpretation of outcome data are limited by concerns with the internal validity and applicability to the Canadian context.

Discussion

Summary of Available Evidence

One phase III study (HERCULES, double-blind RCT, N = 145) submitted by the sponsor is included in this systematic review. The objective of HERCULES was to evaluate the efficacy and safety of caplacizumab in patients with aTTP. The trial included adult patients (≥ 18 years of age) with a clinical diagnosis of aTTP that presented with both thrombocytopenia and microscopic evidence of red blood cell fragmentation. Patients were excluded if they had a platelet count of more than 100 × 10^9/L at screening, had suspected thrombotic microangiopathies that were not associated with aTTP (such as hemolytic uremic syndrome), or if they had congenital TTP. Patients who had clinically significant active bleeding or a high risk of bleeding or were receiving chronic treatment with anticoagulants that could not be stopped safely were also excluded. Eligible patients were randomized to receive caplacizumab 10 mg or placebo, in addition to standard of care, which consisted of PEX and corticosteroid treatment and other immunosuppressives. The double-blind treatment periods consisted of a daily PEX period and a 30-day post–daily PEX period. A treatment extension of seven to 28 days with caplacizumab or placebo was allowed for patients with risk factors for relapse of the presenting TTP episode. During the treatment period for HERCULES, in the case of first exacerbation or relapse of the presenting TTP episode, patients would receive open-label caplacizumab together with daily PEX, irrespective of the initial treatment allocation. The primary efficacy outcome of this study was time to platelet count response, which was defined as an initial platelet count of 150 × 10^9/L or higher with the subsequent stopping of daily PEX within five days. Other efficacy outcomes included prevention of recurrence of aTTP, prevention of refractory aTTP, prevention of major thromboembolic events, normalization of organ damage markers, and reduced length of ICU or hospital stays related to TTP episodes. Harm outcomes associated with the use of caplacizumab were also examined.

The major limitations of HERCULES include potential biases of the study results due to an imbalance of patients' baseline characteristics, uncertainty around the validity of using platelet count for treatment effect evaluation, substantial and disproportional missing data for some efficacy outcomes, underpowered subgroup analyses, and a lack of statistical testing for some of the secondary efficacy end points. Subgroup analysis and sensitivity

analysis were performed; however, the results should be interpreted with caution, given the small sample size. Long-term clinical benefits and harms in the HERCULES results could not be explored due to the trial's short duration.

Interpretation of Results

Efficacy

Four TTP-related deaths were recorded during the overall study period. One patient from the caplacizumab group died during the drug-free follow-up period. Three patients from the placebo group died during the daily PEX period. One death from the placebo group was considered possibly related to the study drug (through blinded assessment), and all other deaths were considered not related to any of the treatments. The results implied that the risk of TTP-related death was higher in patients not treated with caplacizumab. The clinical experts consulted for this review indicated that the mortality in the placebo group (patients received PEX and corticosteroids) reflected those in an optimal trial condition and the mortality rate would be much higher in the real world. The sponsor provided an integrated efficacy analysis that included all randomized patients in HERCULES and TITAN. The results showed a reduction in the mortality rate in the caplacizumab groups, where one patient (0.9%) died compared with five patients (4.5%) in the placebo groups. However, this was a post hoc analysis and the data were published as an abstract. It is unclear whether the data pooling was pre-specified, and there were no details provided on the methods of pooling. The data are suggestive of a survival benefit with caplacizumab but insufficient for drawing a conclusion.

During the overall study period, treatment with caplacizumab was related to a shorter duration of PEX therapy compared with placebo (mean days on PEX = 5.8, SE = 0.5 for caplacizumab and 9.4, SE = 0.8 for placebo). Treatment with caplacizumab was also associated with reduced total PEX volume compared with placebo (21.3, SE = 1.6 L versus 35.9, SE = 4.2 L, respectively). According to the clinical experts consulted for this review, the between-group differences in the number of days on PEX and the PEX volume were considered clinically relevant. Reduction in the use of PEX is an important clinical outcome for patients.

Recurrence of aTTP, either a relapse or exacerbation, was measured in different study periods. Relapses occurred after the 30-day post–daily PEX period; however, only relapses within the overall treatment period were taken into account in the assessment of the key secondary efficacy end points in HERCULES and ranked second in the statistical test hierarchy. During the overall study period, a statistically significantly lower percentage of patients in the caplacizumab group (nine patients [12.7%]) compared with the placebo group (28 patients [38.4%]) experienced a recurrence of aTTP, either an exacerbation or a relapse. Exacerbations occurred in three patients (4.2%) treated with caplacizumab and 28 patients (38.4%) treated with placebo; relapses occurred in six patients (9.1%) treated with caplacizumab but in zero patients in the placebo group. The low recurrence of aTTP was attributed to the lower incidence of aTTP exacerbation in the caplacizumab group.

Treatment with caplacizumab was associated with faster normalization of organ damage markers (LDH, cTnI, and serum creatinine) for patients with aTTP compared with placebo. The median time to normalization was 2.86 days (95% CI, 1.93 to 3.86) in the caplacizumab group and 3.36 days (95% CI, 1.88 to 7.71) in the placebo group, respectively. However, the between-group differences could not be considered statistically

significant because the hierarchical statistical analysis plan failed to demonstrate statistical significance at a higher-order comparison.

During the overall treatment period, the number of patients experiencing major thromboembolic events was similar between the caplacizumab group (six patients [8.5%]) and the placebo group (six patients [8.2%]). HERCULES was not specifically designed to evaluate the effects of caplacizumab on this outcome and the small number of events in the treatment groups makes it difficult to draw conclusions.

During the double-blind treatment period for HERCULES, no patients in the caplacizumab group and three patients (4.2%) in the placebo group were considered to have refractory aTTP. The between-group difference in refractory aTTP was not statistically significant (P = 0.0572). The sponsor provided an integrated efficacy analysis that included all randomized patients in HERCULES and TITAN using the first definition of refractory aTTP (i.e., defined as the absence of platelet count doubling after four days of standard treatment and an LDH > ULN). The sponsor reported that the results showed a statistically significant reduction in the risk of refractory aTTP in the caplacizumab groups (zero patients) compared with the placebo groups (seven patients [6.3%]; P < 0.01), emphasizing that, regardless of the definition used for refractory aTTP, no patients treated with caplacizumab developed refractory disease. However, this was a post hoc analysis and the data were published as an abstract. It is unclear whether the data pooling was pre-specified, and there were no details provided on the methods of pooling. Overall, the data are suggestive of a benefit with caplacizumab for this outcome but insufficient for drawing a conclusion.

Time to platelet response was the primary efficacy end point in HERCULES. Several other outcome measures in HERCULES were defined based on platelet counts, such as recurrence of aTTP and refractory aTTP. A statistically significantly shorter time to normalization of the platelet count was observed in the caplacizumab group (median 2.69 days; 95% CI, 1.89 to 2.83) compared with the placebo group (median 2.88 days; 95% CI, 2.68 to 3.56; P = 0.0099). A hazard ratio of 1.55 (95% CI, 1.10 to 2.20) also suggested that, at any given time point, patients in the caplacizumab group were 1.55 times more likely to achieve a platelet count response compared with those in the placebo group. However, the difference was not considered clinically relevant according to the clinical experts consulted for this review. Caplacizumab acts by preventing platelet adhesion and the formation of microthrombi and thus increases the platelet counts directly. However, caplacizumab does not change the course of the disease or treat the underlying aTTP disease, and potentially masks an indicator of disease activity, which would make it difficult to determine when it is time to taper existing therapies, such as PEX and corticosteroids. The clinical experts indicated that other markers of disease activity (such as LDH, ADAMTS13 activity, and clinical signs of aTTP) would be used. During the follow-up period for HERCULES, when caplacizumab had been discontinued for 30 days or longer after daily PEX cessation, TTP relapses occurred in six patients (9.1%) in the caplacizumab group compared with no patients in the placebo group, which is consistent with the waning of the direct masking effect that caplacizumab has on platelet counts following treatment discontinuation. In addition, it is unknown how much of the gain in platelet counts can be translated into improvement in clinical outcomes. Approaches other than platelet counts, such as time to next treatment or schistocyte counts, may be considered to thoroughly evaluate the disease and treatment effect.

During the overall study period, numerical differences in change from baseline in favour of caplacizumab have been observed for neurological assessment and cognitive function assessment, suggesting potential benefits of the treatment on these outcomes. In addition, patients treated with caplacizumab reported shorter ICU days and hospitalization compared with those treated with placebo. These outcomes are important to both patients and clinicians. However, in HERCULES, these outcomes were not included in the statistical testing hierarchy and no formal statistical tests were performed on them. A substantial amount of missing data in the cognitive assessment was also an issue in interpreting the results. The significance of treatment effect on these outcomes cannot be determined.

For some of the outcome measures, both mean and median were reported, for example, the outcome of reduction in use of PEX. [redacted]. The discrepancy in study findings when measured with mean or median and the wide range associated with the medians suggest a skewed data distribution for patient variation in response, which also reflects the variability in the natural history of the disease, thereby making it difficult to interpret the study findings. The range of distribution for use of PEX was narrower for caplacizumab than for placebo, suggesting a more consistent effect in the caplacizumab group. According to the clinical experts consulted for this report, the effect on treatment for patients with more severe outcomes (higher values, typically) are of particular interest when treating patients with aTTP. This suggests that the comparison of means would be of greater interest than medians for these outcomes, since the mean will be more sensitive to extreme values.

A phase II single-blind RCT (TITAN) provided supportive evidence for treatment with caplacizumab. The efficacy of caplacizumab compared with placebo was demonstrated based on confirmed platelet response, which was the primary outcome in this study. Patients treated with caplacizumab were more likely to reach a confirmed platelet response compared with placebo based on a hazard ratio of 2.20 (95% CI, 1.28 to 3.78) that was statistically significant (P = 0.005).

Harms

During the overall study period, almost all patients reported AEs in HERCULES: 97.2% in the caplacizumab group and 97.3% in the placebo group. The majority of the AEs were of mild or moderate severity. The common AEs reported in the caplacizumab group were epistaxis, headache, gingival bleeding, urticaria, pyrexia, fatigue, nausea, and TTP episodes. In the placebo group, TTP episodes, rash, and contusion were commonly reported. In the open-label caplacizumab therapy period, AEs were reported in 89.3% of patients. Catheter-site hemorrhage, epistaxis, gingival bleeding, and gastrointestinal symptoms were commonly reported.

SAEs were reported in 28 patients (39.4%) in the caplacizumab group and 39 patients (53.4%) in the placebo group during the overall study period. TTP episodes were the most commonly reported SAEs, and the incidence of TTP episodes was higher in the placebo group (39.7%) than in the caplacizumab group (12.7%), potentially reflecting differences in efficacy between the treatment groups. During the open-label caplacizumab therapy, seven patients (25%) reported SAEs.

During the overall study period, five patients (7.0%) treated with caplacizumab and nine patients (12.3%) treated with placebo withdrew from the study or from treatment due to AEs. During the open-label caplacizumab therapy period, one patient withdrew due to AEs.

Three patients in the placebo group died during the daily PEX treatment period. One patient in the caplacizumab group died in the follow-up period.

In terms of AEs of particular interest, during the overall study period, the risk of bleeding events was similar between treatment groups: 49 patients (69%) in the caplacizumab group and 49 patients (67.1%) in the placebo group. Hypersensitivity was experienced by [redacted] in the caplacizumab group and [redacted] in the placebo group. Anti-drug antibodies were found in two patients (2.8%) in the caplacizumab group and one patient (1.4%) in the placebo group.

During the open-label treatment with caplacizumab, [redacted].

Results from the TITAN study indicated that almost every patient experienced at least one AE and more than half of them experienced at least one SAE. The most common AE and SAE was TTP episodes. The most common AEs following TTP in the caplacizumab group were headache, epistaxis, and nausea, which was consistent with the results from HERCULES.

Conclusions

One phase III, double-blind, placebo-controlled, randomized trial provided evidence on the efficacy and safety of caplacizumab in adult patients with aTTP. Patients who received caplacizumab in addition to standard therapy (PEX and immunosuppressants) showed benefits in reducing the duration and volume for PEX and reducing the frequency of aTTP exacerbations compared with placebo. There were no data on the impact of caplacizumab on subsequent aTTP recurrence beyond the trial observation period. Although only one of the four deaths in the trial occurred in the caplacizumab group and was considered by the blinded assessors as unrelated to treatment, the study was designed to specifically assess survival. Therefore, it remains uncertain what the impact of caplacizumab is on survival and additional research is required. Caplacizumab improved platelet counts but it is unclear what the clinical relevance of this finding is. Almost all study participants reported TEAEs. A high frequency of bleeding events occurred in the caplacizumab group, while patients who received placebo reported more TTP episodes. Most of the reported AEs were mild to moderate in intensity. A phase II single-blind RCT provided evidence to support the effect of caplacizumab on platelet response. The safety results in this trial were consistent with those in the phase III trial.

Conclusions regarding the long-term efficacy and safety of caplacizumab in patients with aTTP are lacking due to the short duration of treatment; in addition, the long-term results can be complicated by the use of open-label caplacizumab in some patients.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	October 9, 2019
Alerts:	Bi-weekly search updates until project completion
Study Types:	No filters were applied to limit retrieval by study type
Limits:	Publication date limit: none Language limit: none Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word
.dq	Candidate term word (Embase)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(cablivi* or caplacizumab* or ALX-0081 or ALX0081 or ALX-81 or ALX81 or ALX-0681 or ALX0681 or 2R27AB6766).ti,ab,kf,ot,hw,nm,rn.
2	1 use medall
3	*caplacizumab/ or (cablivi* or caplacizumab* or ALX-0081 or ALX0081 or ALX-81 or ALX81 or ALX-0681 or ALX0681).ti,ab,kw,dq.
4	3 use oemezd
5	4 not (conference review or conference abstract).pt.
6	2 or 5
7	remove duplicates from 6

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search terms: Cablivi/caplacizumab	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms: Cablivi/caplacizumab	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	

Grey Literature

Dates for Search:	October 2019
Keywords:	Cablivi/caplacizumab; acquired thrombotic thrombocytopenic purpura (aTTP)
Limits:	Publication years: none

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals

Appendix 2: Excluded Studies

Table 27: Excluded Studies

Reference	Reason for Exclusion
No studies were excluded.	

Appendix 3: Detailed Outcomes Measures

Table 28: Summary of Integrated Efficacy Analyses, Including Patients From HERCULES and TITAN

	Caplacizumab N = 108	Placebo N = 112
Primary end points Time to platelet count response: • platelet count normalization ratio (95% CI) • P value	 1.65 (1.24 to 2.20) 0.0006	
Secondary end points Percentage of patients experiencing at least one of the following events while on DB or SB study drug treatment, n (%): • TTP-related death • major thromboembolic event • TTP recurrence (exacerbation)	14 (3.0) 0 8 (7.4) 6 (5.6)	53 (47.3) 4 (3.6) 14 (12.4) 39 (34.8)
P value	< 0.0001	
TTP recurrence during the entire study period, n (%)	19 (17.6)	39 (34.8)
P value	0.0040	
Refractory to treatment, n (%)	0	7 (6.3)
P value	0.0089	
Mortality rate		
During the DB or SB treatment period, n (%), P value	0 (0)	4 (3.6), P = 0.0477
During the entire study period, n (%), P value	1 (0.9)	5 (4.5), P = 0.1086
Number of days of PEX during the DB or SB treatment period, mean (SD)	6.5 (4.5)	10.4 (7.7)

CI = confidence interval; DB = double-blind; PEX = plasma exchange; SB = single-blind; SD = standard deviation; TTP = thrombotic thrombocytopenic purpura.

Source: Peyvandi (2018) abstract[23] from *Integrated Efficacy Results From the Phase II and Phase III Studies With Caplacizumab in Patients with Acquired Thrombotic Thrombocytopenic Purpura*, HighWire Press, American Society of Hematology, volume 132, Supplement 1, 2018. Republished with the permission of the American Society of Hematology. Permission conveyed through the Copyright Clearance Center Inc.

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and minimal important difference):

- SMMSE
- GCS

Findings

Table 29: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
SMMSE	30-point questionnaire to assess cognitive impairment in older adults.	Reliability was demonstrated in elderly patients by an intra-rater ICC of 0.92 and an inter-rater ICC of 0.89 to 0.90.[27] This does not necessarily translate to use in patients with aTTP. Evidence of validity and responsiveness were not identified.	Not identified in the literature for patients with aTTP or the general population. 1.4 for patients with Alzheimer disease.[28]
GCS	A 15-point scale comprising three parameters: • best eye response (scored from 1 to 4) • best verbal response (scored from 1 to 5) • best motor response (scored from 1 to 6).	A systematic review provided evidence of reliability;[29] however, no evidence of reliability, validity, or responsiveness was identified for patients with aTTP.	Not identified in the literature.

aTTP = acquired thrombotic thrombocytopenic purpura; GCS = Glasgow Coma Scale; ICC = intraclass correlation coefficient; MID = minimal important difference; SMMSE = Standardized Mini-Mental State Examination.

Standardized Mini-Mental State Examination

The SMMSE is an instrument used to assess cognitive impairment in older adults.[21,22] Multiple domains of cognitive function are evaluated, including orientation to time and place, registration, concentration, short-term recall, naming familiar items, repeating a common expression, and ability to read and follow instructions (write a sentence, construct a diagram, and follow a three-step verbal command.)[21]

The SMMSE is scored based on a 30-point questionnaire that takes approximately 10 minutes to complete. Among the general population, a score of 26 to 30 is considered normal, 20 to 25 indicates possible mild cognitive impairment, 10 to 20 is considered moderate cognitive impairment, and 0 to 9 corresponds to severe cognitive impairment.

The SMMSE is suitable for use in various settings of care, such as the doctor's office, community clinics, acute care settings, and long-term care settings; however, it is important that it be administered correctly to ensure valid and reliable results.[21] A set of guidelines has been developed to aid the correct administration of the test.[30]

Reliability of the SMMSE was demonstrated in a study by Molloy et al.[27] The study included 48 elderly residents from a nursing home and a chronic care hospital unit who completed the SMMSE three times, each one week apart. The intraclass correlation was analyzed to examine reliability. Briefly, the SMMSE demonstrated almost perfect[31] reliability based on an intraclass correlation coefficient of 0.92 for the same raters and 0.89 to 0.90 for different raters.

There are certain limitations to be aware of when using the SMMSE, such as the age and level of education of the patient.[10,21] A patient that is more highly educated is likely to score higher on the SMMSE than their level of cognitive function suggests. Conversely, patients may score lower due to a language barrier, suggesting a score lower than their level of cognitive function.[21]

Evidence of validity, reliability, and responsiveness of the SMMSE in patients with aTTP was not identified. Although the SMMSE is a well known and widely used tool, it is primarily used for older adults with cognitive impairment and does not directly apply to patients with aTTP, which is a limitation of its use in the caplacizumab trials. Further, an MCID was not identified for the general population or patients with aTTP; however, the clinical experts consulted for this review reported an MCID of between one and two points is commonly used for patients with dementia, Alzheimer disease, and other neurodegenerative diseases. This was supported by an MCID of 1.4, which was determined based on expert opinion and distribution-based MCIDs using data from patients participating in the DOMINO trial (RCT of donepezil for patients with probable or possible moderate or severe Alzheimer disease.)[28,32]

Glasgow Coma Scale

The GCS was designed to assess the level of consciousness of a patient with acute brain injury. It assesses three aspects of behaviour (parameters): motor responsiveness, verbal performance, and eye opening, which are each measured independently.[33] The total score ranges from three to 15, with three being the worst score and 15 being the best.[10] The three aspects of behaviour are summed to generate a total score. A description of the behaviour-based parameters is summarized below.

Eye opening ("best eye response") is scored from one to four, corresponding to "no eye opening," "eye opening to pressure," "eye opening to sound," and "eyes open spontaneously," respectively. Verbal performance ("best verbal response") is scored from one to five, for "no verbal response," "sounds," "words," "confused," and "oriented." Lastly, motor responsiveness is scored from one to six, corresponding to "no motor response," "extension," "abnormal flexion," localizing," and "obeys commands," respectively.[10]

A total score of 13 or higher indicates mild brain injury, a score of nine to 12 indicates moderate injury, and a score of eight or less indicates severe brain injury.[10] It is recommended that the scores of each parameter be reported along with the total score to provide a more accurate description of the severity of the patient's condition, as different scores for the individual parameters can provide the same total score with different clinical implications.[34]

Evidence of validity, reliability, and responsiveness have not been identified for patients with aTTP; however, a systematic review of the GCS reported excellent reliability of the instrument based on 52 relevant studies in a heterogenous population of patients, settings, and characteristics of observers.[29] Nonetheless, there is a lack of evidence to support the use of the GCS in patients with TTP.

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