CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

CAPLACIZUMAB (CABLIVI)

Indication: For the treatment of adults with acquired thrombotic thrombocytopenic purpura (aTTP) in combination with plasma exchange (PE) and immunosuppressive therapy (IST).

Sponsor: sanofi-aventis Canada Inc.

Recommendation: Do Not Reimburse

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that caplacizumab not be reimbursed for the treatment of adults with acquired thrombotic thrombocytopenic purpura (aTTP) in combination with plasma exchange (PE) and immunosuppressive therapy (IST).

Rationale for the Recommendation

As outlined in the 2020 CDEC final recommendation for caplacizumab one phase III, double-blind, randomized controlled trial (RCT) (HERCULES; N = 145) in adults with aTTP receiving PE and IST demonstrated that treatment with caplacizumab statistically significantly reduced the time to normalization of platelet count, however, the study was not designed to assess the effects of caplacizumab on the clinically important outcomes of survival, reduction in organ damage, health care use, or long-term recurrence of aTTP. Given caplacizumab's mechanism of action, CDEC could not determine the clinical magnitude of the correlation between time to normalization of platelet count with the aforementioned clinical outcomes. As part of the evidence base for the resubmission, CDEC considered other studies including a long-term follow up study [Post-HERCULES; N = 104], a post-hoc integrated analysis of data from the HERCULES and TITAN trials [N = 220], and several real-world evidence [RWE] studies. Several methodological limitations in the reviewed studies precluded CDEC from determining whether caplacizumab provides clinically meaningful value compared with PE plus IST alone. Further, no definitive conclusion could be reached regarding the effects of caplacizumab on health-related quality of life (HRQoL) from the Post-HERCULES trial, given the exploratory nature of the analyses, the open-label design, variable rates of missing data, and uncertainty in the measurement properties of the patient-reported outcomes instruments in patients with aTTP.

Patients described their aTTP as having a significant impact on their quality of life and identified a need for effective treatments that improve survival and quality of life, prevent disease complications, reduce recurrence rates, reduce the need for PE, and have fewer side effects. While recognizing the need for additional effective treatment options for this patient population, there was uncertainty whether caplacizumab met these important therapeutic needs given the limitations associated with the evidence reviewed.

Discussion Points

- CDEC noted that although aTTP is a rare and serious condition, the nature of the disease and administration of current therapies does permit for well-designed randomized trials to be conducted.
- An outcome identified as important to patients is a reduction in the risk and rate of experiencing relapses of aTTP. The design and duration of HERCULES were insufficient to assess the effects of caplacizumab on the rate of relapse (i.e., recurrent thrombocytopenia occurring after the 30-day post-daily PE period) beyond the trial's duration. The Post-HERCULES study (a 3-year follow-up study of patients who completed HERCULES) evaluated long-term aTTP relapse in patients who did not experience an aTTP recurrence in the HERCULES study or prior to the beginning of the Post-HERCULES study (i.e., efficacy intention-to-observe [ITO] population). While the data from the Post-HERCULES study did not provide a signal that caplacizumab resulted in more frequent aTTP relapses post PE discontinuation compared to placebo, CDEC considered the data insufficient to draw firm conclusions. The Post-HERCULES study was not designed to provide robust evidence on long-term aTTP relapse rates and patients who experienced more than 2 episodes of aTTP were not analyzed in the efficacy analyses of aTTP recurrence in the efficacy ITO population which assessed patients up to their first recurrence.
- A post-hoc integrated analysis of HERCULES and TITAN data evaluated survival, healthcare use, organ damage, and refractory aTTP. The committee noted that results appeared overall consistent with those of the two individual studies. However, given it was unclear if the data pooling was appropriate and the lack of inferential statistical testing among other limitations, CDEC concluded that the data were insufficient to draw conclusions.
- RWE studies (comparing caplacizumab-treated patients with historical controls who received standard of care) provided supportive evidence on survival, health care use, and refractory aTTP. However, due to the potential for biased patient selection and intergroup differences in measured and/or unmeasured confounding variables, no firm conclusions could be drawn on the results of these studies.
- According to clinical experts consulted by CADTH, the percentage of patients who received rituximab in the HERCULES study and the RWE cohort studies was higher than what is expected in Canada. Given that 40% of patients in the overall HERCULES trial period received caplacizumab in addition to rituximab (and PE plus corticosteroids), it is unclear if the observed effects of caplacizumab in the trial would be observed in Canadian practice. The committee agreed that currently there is insufficient evidence to determine the effect of concomitant use of rituximab on the overall study outcomes.
- CDEC discussed that the HERCULES trial suggested that treatment with caplacizumab may reduce the total PE volume and decrease duration of PE therapy compared with placebo. However, given that no prespecified statistical comparisons were conducted in the analysis of these data, imbalances existed in the baseline characteristics of the two groups, and there was a lack of long-term clinical outcome data, CDEC found it difficult to interpret these findings. The committee discussed that results from the integrated analyses and the RWE studies were supportive of a reduced need for PE. However, given the aforementioned limitations with both data sources, CDEC concluded that the data were insufficient to draw firm conclusions.
- CDEC considered that there is currently an unmet need for treatment options that improve patients' survival while preventing aTTP complications and their sequelae and associated disabilities. CDEC acknowledged input from the clinical experts that this unmet need is primarily in patients who have refractory or recurrent aTTP and in patients who are critically ill with end-organ dysfunction. Based on available evidence, CDEC concluded that currently there is insufficient evidence to inform a recommendation on a subset of patients most likely to respond to caplacizumab in combination with PE and IST.

Background

Thrombotic thrombocytopenic purpura (TTP) is an ultra-rare blood disorder caused by reduced enzymatic activity of the von Willebrand factor (vWF)-cleaving protease, a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13), resulting in an inability to cleave high molecular weight vWF multimers and as a consequence formation of platelet-rich blood clots in small vessels (thrombotic microangiopathy). TTP is a medical emergency and acquired TTP (aTTP; driven by autoantibodies against ADAMTS13) is the dominant form. Mortality is estimated at approximately 10% to 20%; in addition, thrombotic complications and their sequelae contribute to persistent cognitive and physical difficulties that can be life-altering in some patients, compromising health-related quality of life (HRQoL). After the presenting episode, recurrence of aTTP (exacerbation: recurrence within 30 days of cessation of plasma exchange [PE]; relapse: recurrence after 30 days of cessation of PE) will occur in up to half of patients, while refractory aTTP (absence of platelet count increase following treatment) will occur in approximately 10% of patients. The incidence of aTTP is estimated at approximately 2 to 4 cases per million population per year (approximately 5.5 cases per million adults); approximately [redacted] patients with TTP were treated in Canada in 2018. According to the clinical experts consulted by CADTH, current management of aTTP in Canada involves PE and immunosuppression with corticosteroids. In Canada, rituximab is typically not used upfront and is administered to patients with aTTP exacerbations, relapsed aTTP, or refractory aTTP. The main goals of treatment are to prolong life and avoid mortality while preventing thrombotic complications and associated disabilities.

Caplacizumab has been approved by Health Canada for the treatment of adults with acquired thrombotic thrombocytopenic purpura (aTTP) in combination with plasma exchange (PE) and immunosuppressive therapy. Caplacizumab is a bivalent humanized nanobody and an antithrombotic agent/platelet aggregation inhibitor. It is available as a powder for solution (11 mg) and the dosage recommended in the product monograph is 11 mg (intravenous [IV] and subcutaneous [SC] injections on day 1 of PE followed by daily SC injections during PE and for a minimum of 30 days after cessation of PE).

Submission History

Caplacizumab was initially reviewed by CADTH for the treatment of adults with aTTP in combination with PE and immunosuppressive therapy and received a negative funding recommendation from the Canadian Drug Expert Committee (CDEC) on September 1, 2020. The original CADTH review of caplacizumab included one phase 3, double-blind (DB) randomized controlled trial (RCT) (HERCULES, N=145) and supportive evidence from one phase 2, multicenter, single-blind (SB), parallel design, placebo-controlled RCT (TITAN, N=75) that evaluated the efficacy and safety of caplacizumab in adult patients with aTTP. Key reasons for the recommendation included insufficient evidence of clinically important outcomes (e.g., survival, organ damage, health care use, or long-term aTTP recurrence), lack of long-term clinical outcome data, lack of an identifiable subpopulation most likely to benefit from treatment, generalizability to Canadian clinical practice, and absence of HRQoL data.

The drug was resubmitted for review by the sponsor on the basis of the availability of new data in order to address the evidence gaps identified by CDEC with the 2020 review. The sponsor submitted a prospective long-term follow-up study of patients who completed HERCULES (Post-HERCULES), a variety of post-hoc analyses including an integrated analysis of data from HERCULES and TITAN, and several real-world evidence (RWE) studies including comparisons of caplacizumab-treated patients with historical controls who received standard of care (SoC) alone in France and the United Kingdom (UK).

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- A review of 1 phase 3 RCT trial (HERCULES) in adult patients with aTTP and its prospective, long-term follow-up study (Post-HERCULES) in patients who completed the HERCULES trial; supportive data from 1 phase 2 RCT (TITAN) in patients with aTTP; supportive data from a post-hoc integrated analysis of HERCULES and TITAN trials; and supportive data from 2 RWE cohorts from France and the UK.
- Patients' perspectives gathered by one patient group, the Answering TTP Foundation
- Input from public drug plans and cancer agencies that participate in the CADTH review process
- Input from 2 clinical specialists with expertise diagnosing and treating patients with aTTP

- Input from 1 clinician group, the Canadian Apheresis Group (CAG)
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

One patient group, the Answering TTP Foundation, provided input for this review. The group conducted an online survey in May and June of 2022 (N=49 respondents including 31 patients with aTTP, 16 family members, caregivers, or friends of patients with aTTP, one healthcare professional, and one researcher). Most (80%) survey respondents were women and most (90%) were Canadian. Approximately half of respondents (48%) had experienced at least one relapse. Patients highlighted delays in diagnosis and treatment as well as the negative impacts of serious and/or frequent symptoms of aTTP (e.g., bruising, fever, fatigue, migraine, confusion, abdominal pain, bleeding, shortness of breath, vision loss, and jaundice) which impose heavy burdens on mental health (e.g., anxiety, depression, and panic attacks). A subset of patients experienced incapacitating or life-threatening complications of aTTP including stroke, myocardial infarction, and kidney problems. Nearly all patients had experience with PE and corticosteroids while approximately two thirds (65%) had experience with rituximab. Respondents described the challenges of current treatments including lengthy hospital stays, side effects of corticosteroids, and the inconvenience of daily PE; in addition, available treatments are costly, require time off from work, and may require travel to a major centre for access. Respondents identified an unmet need for treatments that can reduce the risk of death or disability from aTTP and ease the mental and emotional burdens of disease (e.g., continuous fear of relapse, risk of treatment failure and impacts on social life and career goals). Specifically, respondents valued new treatments that enable patients to survive an aTTP crisis and reduce the likelihood of disease recurrence, thereby reducing the patient's emotional uncertainty in the early stages of a TTP episode and improving peace of mind during remission. As well, respondents noted that a reduction in the number of PE treatments and ability to plan for the future were important when considering treatment options. Approximately one third (34%) of respondents had experience with caplacizumab and felt that the drug had contributed to shorter hospitalization, faster remission, and prevention of further disease.

Clinician Input

Input from Clinical Experts Consulted by CADTH

Two clinical specialists with expertise in the diagnosis and management of aTTP provided input for this review. The clinical experts stated that while currently available treatments (PE plus immunosuppression with corticosteroids with or without rituximab) are effective in many patients, not all patients manifest durable responses and thus experience persistent or recurrent thrombotic microangiopathy, which can lead to thrombotic complications and, potentially, mortality. According to the clinical experts, there is an unmet need for additional treatment options especially for patients with aTTP recurrence or refractory aTTP. The clinical experts relayed that caplacizumab would be administered in combination with PE and immunosuppressive therapy. The clinical experts felt that because some patients respond well to PE and immunosuppressive therapy, caplacizumab may be a reasonable option to be reserved for patients with aTTP recurrence or refractory aTTP as these patients currently have limited treatment options. The clinical experts acknowledged that it is currently unclear if delaying access to caplacizumab may impact its efficacy. The HERCULES trial was designed to evaluate the upfront use of caplacizumab in combination with PE and immunosuppressive therapy. The clinical experts also felt that upfront treatment with caplacizumab would be considered in high-risk patients who have neurologic or cardiac abnormalities (including elevated troponin) or are otherwise critically ill. The clinical experts acknowledged that currently there is insufficient evidence to identify patients who are more likely to respond to caplacizumab in combination with PE plus immunosuppression. The clinical experts stated that clinically meaningful responses to caplacizumab plus PE and immunosuppression would be defined by normalization of platelet count (complete blood count) and lactate dehydrogenase (LDH) level. Reticulocyte count, unconjugated bilirubin, hemoglobin, haptoglobin, creatinine, ADAMTS13 activity, and ADAMTS13 autoantibody levels should also normalize. The clinical experts relayed that although the ultimate mechanistic goal of therapy is to normalize ADAMTS13 activity, results of ADAMTS13 testing are generally not readily available in a timely manner, as compared to

platelet count. According to the clinical experts, PE is typically discontinued after 5 days if platelet count, LDH, and other markers are normalized. Patients are then typically monitored for 1 to 2 days while in hospital to see if their platelet counts drop again or if the hemolytic markers show signs of aTTP recurrence. If there is no evidence of aTTP recurrence, patients are typically discharged from hospital with a corticosteroid taper plan and close outpatient follow-up. The clinical experts stated that in patients receiving caplacizumab who develop aTTP recurrence or refractory aTTP would be discontinued from therapy, as would patients with serious toxicities such as clinically significant bleeding. The clinical experts relayed that one of the challenges of using caplacizumab is that it directly increases platelets through its mechanism, potentially masking an indicator of aTTP disease activity, which would make it difficult to determine when it is time to taper PE.

Clinician Group Input

Clinician group input was received from the Canadian Apheresis Group (CAG), with five clinicians contributing to the submission. No major contrary views from those provided by the clinical experts consulted by CADTH for this review were presented. The clinician group echoed the inability of current treatments to accomplish the goals of therapy (avoid mortality and prevent thrombotic complications) in all patients and the unmet need for additional treatment options for patients with aTTP exacerbations, relapsed aTTP, and refractory aTTP as well as patients at high risk of mortality and/or organ damage. The clinician group also highlighted the unmet need for drugs that can rapidly inhibit platelet aggregation while waiting for PE and immunosuppression to take effect.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for caplacizumab:

- Considerations for initiation of therapy
- Considerations for continuation or renewal of therapy
- Considerations for discontinuation of therapy
- Considerations for prescribing of therapy
- Generalizability of trial populations to the broader populations in the jurisdictions
- Care provision issues
- System and economic issues

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

The phase 3 HERCULES trial and phase 2 TITAN trial were reviewed in the original CADTH Clinical Review Report for the original caplacizumab submission in 2020 and were considered relevant evidence for this review. The primary outcome in both studies was time to platelet response. Statistically tested secondary outcomes in HERCULES included the composite endpoint of aTTP-related events (aTTP-related death, recurrence of aTTP, or at least one major thromboembolic event), proportion of patients with aTTP recurrence, proportion of patients with refractory aTTP, and time to normalization of all three of the organ damage markers LDH, cardiac troponin, and serum creatinine. There were no statistically tested secondary outcomes in TITAN. Both studies documented statistically significant differences in time to platelet count response that were viewed by the clinical experts consulted by CADTH for the previous review as too small to be clinically relevant. In the HERCULES study, the proportion of patients randomized to receive caplacizumab who experienced recurrence during the HERCULES overall study period was statistically significantly lower compared with patients randomized to receive SoC. Differences between study randomization arms in the proportion of patients with refractory aTTP were not statistically significant, precluding further statistical testing. The duration and volume of daily PE was shorter in the

caplacizumab arm, which the clinical experts consulted by CADTH felt was encouraging and potentially clinically relevant. In addition, duration of hospitalization and ICU stay was shorter in the caplacizumab arm, but missing data and absence of statistical testing prevented interpretation of these results. Analysis of mortality and time to normalization of organ damage markers numerically favoured caplacizumab but without formal, prespecified statistical testing, these differences could not be interpreted.

One phase 3, prospective, long-term follow-up study of adult patients with aTTP who completed the HERCULES study (Post-HERCULES, N=104) contributed new evidence to this resubmission. The objectives of Post-HERCULES were to evaluate long-term safety and efficacy of caplacizumab, to evaluate the safety and efficacy of repeated use of caplacizumab in participants who experienced a recurrence of aTTP, and to characterize the long-term clinical impact of aTTP. Following the final 4-week follow-up visit in HERCULES, adult patients with aTTP were invited to enrol in Post-HERCULES within 1 month. Patients who were not able or willing to comply with study protocol procedures or who enrolled in a clinical study with another investigational drug or device were excluded. Following enrollment at 43 centres in Europe, the US, Canada (three centres), and Israel, patients were followed for a period of 3 years. Patients attended twice-yearly visits, starting with a baseline visit coinciding with or occurring within 1 month of the final 28-day follow-up visit in HERCULES. During the 3-year follow-up period, patients could receive open label (OL) caplacizumab in combination with PE and immunosuppression (administered as in HERCULES, except that one PE could be given prior to initiation of caplacizumab) for aTTP recurrence (defined as recurrence of thrombocytopenia requiring initiation of daily PE).

The overall intent to observe (ITO) population (N = 104) was used for analysis of safety. The efficacy ITO population (N = 78; patients within the overall ITO population who had not experienced aTTP recurrence in HERCULES or prior to the beginning of post-HERCULES) was used for analysis of efficacy based on twice-yearly follow-up visits. The recurrence population (N = 19; patients within the overall ITO population who experienced at least one aTTP recurrence during Post-HERCULES) was used for analysis of data collected during recurrence periods.

All patients who completed the HERCULES study (n=108) were eligible for Post-HERCULES, of whom 104 (96.3%) participated. Approximately two thirds of participants in Post-HERCULES were women (71.2%), approximately two thirds (70.2%) were White, and the average age was 47.5 years. Note that patients were disease-free at the Post-HERCULES baseline and thus the average ADAMTS13 activity was 62.1%.

Efficacy Results

In the efficacy ITO population, consisting of patients who completed HERCULES, enrolled in Post-HERCULES, and had not experienced an aTTP recurrence in either HERCULES or prior to the beginning of Post-HERCULES, aTTP-related events (aTTP-related death, recurrence of aTTP, or major thromboembolic events) occurred in four patients (8.2%) randomized to receive caplacizumab in HERCULES and in 11 patients (37.9%) randomized to receive SoC alone in HERCULES. No patients randomized to receive caplacizumab in HERCULES and one patient (3.4%) randomized to receive SoC in HERCULES died during Post-HERCULES. Four patients (8.2%) randomized to receive caplacizumab in HERCULES and eight patients (27.6%) randomized to receive SoC in HERCULES experienced recurrence of aTTP during Post-HERCULES. Four patients (8.2%) randomized to receive caplacizumab in HERCULES and eleven patients (37.9%) randomized to receive SoC in HERCULES experienced major thromboembolic events during Post-HERCULES; major thromboembolic events other than aTTP occurred in no patients randomized to receive caplacizumab in HERCULES and in three patients (10.2%) randomized to receive SoC in HERCULES.

Harms Results

In the overall ITO population, 68 patients (90.7%) treated with caplacizumab in HERCULES and 26 patients (89.7%) treated with SoC only in HERCULES experienced adverse events during Post-HERCULES. Twenty-eight patients (37.3%) treated with caplacizumab in HERCULES and 16 patients (55.2%) treated with SoC only in HERCULES experienced serious adverse events during Post-HERCULES. No patients treated with caplacizumab and one patient (3.4%) treated with SoC only in HERCULES died during Post-HERCULES. Sixteen patients (21.3%) treated with caplacizumab in HERCULES and nine patients (31.0%) treated with SoC only in HERCULES experienced at least one bleeding event during Post-HERCULES (based on Standardized Medical Dictionary for Regulatory Affairs Query “Haemorrhage” excluding the Preferred Term “aTTP”).

Critical Appraisal

Many of the internal validity issues of HERCULES affect Post-HERCULES as well. Only patients who completed HERCULES (108 of 145, 74.5%) were eligible for Post-HERCULES, and the study provides no information on patients who discontinued HERCULES. Higher proportions of caplacizumab-naïve patients (n=6, 20.7%) than patients who received caplacizumab in HERCULES (n=5, 6.7%) discontinued the Post-HERCULES study. The clinical experts consulted by CADTH for this review did not expect that any resulting biases would be directional in favour of caplacizumab. Due to variable rates of missing data, lack of formal statistical testing, potential for bias in patient-reported outcomes in an OL study, and uncertainty in the measurement properties of these instruments in patients for aTTP, changes in HRQoL over time and between the arms of the Post-HERCULES efficacy ITO population could not be interpreted.

Many of the external validity issues of HERCULES affect Post-HERCULES as well. The clinical experts consulted by CADTH felt that the Post-HERCULES study population was generally reflective of adults patients with aTTP in Canada. Mortality rates in the HERCULES and post-HERCULES studies were lower than expected in routine clinical practice and patients may have been observed and followed by healthcare teams for aTTP recurrence and/or thromboembolic events more vigilantly compared to real-world practice. The clinical experts consulted by CADTH stated that the duration of follow-up in Post-HERCULES was adequate to assess both early recurrence of aTTP (within the first month of presentation) and later recurrences (which often occur within the 2 years following cessation of PE). In Post-HERCULES, caplacizumab could be administered following up to one administration of PE, but this was not a requirement as it was in HERCULES. Approximately half (six of 13, 46.2%) of patients treated for their first recurrence in Post-HERCULES with caplacizumab received rituximab. The clinical experts consulted by CADTH for this review noted that the proportion of Canadian patients with aTTP who receive upfront rituximab in addition to PE and corticosteroids is not known with certainty but is likely lower than in the post-HERCULES trial. However, the proportion in clinical practice has increased in recent years due to improved access to rituximab.

Indirect Comparisons

No indirect evidence was identified for this review.

Other Relevant Evidence

Six post-hoc analyses were included in the sponsor's resubmission: a publication of an integrated analysis of HERCULES and TITAN as well as four posters and one abstract describing subgroup analyses of HERCULES and Post-HERCULES data by rituximab use in HERCULES, subgroup analyses of HERCULES data by baseline disease severity and time to platelet count response, and a subgroup analysis of patients in HERCULES who had suboptimal responses to PE. Because of their post-hoc design and incomplete description, the results of the posters/abstracts were excluded from the main body of the CADTH clinical report and described in Appendix 4 for reference only.

In addition, a RWE study of a German cohort that was included in the sponsor's submission was not considered by the CADTH Review Team to address an important gap in the evidence due to the lack of a comparison between patients who received caplacizumab and patients who did not receive caplacizumab. Four abstracts describing other RWE cohorts were not described in sufficient detail to enable the CADTH Review Team to rigorously evaluate their conduct and reporting.

Post-Hoc Analyses

Description of Studies

Peyvandi et al. (2021) conducted an integrated analysis of data from the HERCULES and TITAN trials as suggested by the US FDA to increase statistical power for assessing treatment differences in efficacy and safety outcomes. The integrated analysis included all randomly assigned patients from the HERCULES and TITAN studies, which were described in detail in the Clinical Review Report for the initial review of caplacizumab (see Appendix 2). This study provided an additional evaluation of the clinically important outcomes of mortality, organ damage, health care utilization, and refractory aTTP, but did not address long-term aTTP recurrence.

For the primary analysis of time to platelet count response, treatment groups were compared using a 2-sided log-rank test stratified by trial based on Kaplan-Meier analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using a Cox proportional hazards model with time to platelet count response as a dependent variable, treatment group as an independent

variable, and study as a random effect. To compare secondary outcomes (time to normalization of organ damage markers, duration of PE, proportion of patients with aTTP-related death, aTTP recurrence, or major thromboembolic events, and aTTP recurrence) between treatment groups, a stratified Cochran-Mantel-Haenszel test was used as a stratification factor in the trials. Analysis of time to first normalization of organ damage markers was performed as for the primary analysis of time to platelet count response.

Efficacy Results

During blinded study drug treatment, no patients randomized to receive caplacizumab and four patients (3.6%) randomized to receive placebo died; during the overall study periods, one patient (0.9%) randomized to receive caplacizumab and five patients (4.5%) randomized to receive placebo died. The proportion of patients who experienced aTTP-related events (aTTP-related death, major thromboembolic events, or aTTP exacerbation) while receiving blinded study drug treatment was 13.0% in patients randomized to receive caplacizumab versus 47.3% among patients randomized to receive placebo. During blinded study drug treatment, no patients randomized to receive caplacizumab and eight patients (7.1%) randomized to receive placebo had refractory aTTP. Consistent with the individual studies, treatment with caplacizumab resulted in a numerically faster time to normalization of LDH (HR 1.43, 95% CI: 1.04 to 1.96), numerically faster time to normalization of troponin (HR 1.32, 95% CI: 0.86 to 2.04), and numerically faster time to normalization of serum creatinine (HR 1.68, 95% CI: 0.89 to 3.15). During the overall treatment periods, median duration of PE was numerically shorter in patients randomized to receive caplacizumab (5.0 days, range: 1 to 35 days) compared with patients randomized to receive placebo (7.5 days, range: 2 to 46 days). During the treatment-free follow-up periods, 14 patients (13.0%) randomized to receive caplacizumab and no patients randomized to receive placebo experienced aTTP relapses.

Harms Results

The safety data for the integrated safety population were consistent with the results of the individual studies and no new safety signals were identified. Bleeding excluding aTTP occurred in 58.5% of patients treated with caplacizumab and 42.7% of patients treated with placebo. Serious bleeding excluding aTTP occurred in 11.3% of patients treated with caplacizumab and 1.8% of patients treated with placebo.

Critical Appraisal

Overall, the results of the integrated analysis supported and reinforced the consistent numeric improvements in the clinically important outcomes of survival, refractory aTTP, and duration of PE observed in the clinical development program (phase 2 TITAN and phase 3 HERCULES studies). However, internal and external validity issues of the individual HERCULES and TITAN trials affect the integrated analysis as well (see the Clinical Review Report for the initial submission of caplacizumab for details, the executive summary of which is reproduced as Appendix 2). In particular, the clinical experts consulted by CADTH for this review were concerned that the higher proportion of patients in the placebo arm of the integrated population with recurrent rather than initial aTTP may have contributed to poorer outcomes, including higher mortality. In addition, there were several notable differences between the TITAN and HERCULES studies, including the time they were conducted (2010 to 2014 vs. 2015 to 2017) and the administration of caplacizumab (requirement for one prior PE session in HERCULES and the possibility to extend treatment beyond the first 30 days post-PE in HERCULES). Thus, the clinical experts consulted by CADTH for this review relayed their uncertainty that the data from the two studies could be naively pooled. Statistical analyses of integrated data in the study by Peyvandi et al. (2021) were post-hoc, not adjusted for multiple comparisons, and should be interpreted in descriptive and exploratory fashion.

Real-World Evidence

Description of Studies

Three studies of two RWE cohorts of patients treated with caplacizumab from France and the UK are summarized in this report. The RWE studies provided additional supportive evidence regarding the clinically important outcomes of mortality, health care use, and refractory aTTP, but did not address organ damage or long-term aTTP recurrence.

Coppo et al. (2021) prospectively analyzed outcome data for 90 patients with aTTP from France treated from September 2018 to December 2019 with a frontline triplet regimen consisting of PE, immunosuppression with corticosteroids and rituximab, and caplacizumab. Outcomes were compared with 180 historical control patients from the Centre National de Référence sur les

Microangiopathies Thrombotiques (CNR-MAT) registry treated from June 2015 to September 2018 with standard frontline therapy (PE plus corticosteroids, with rituximab as salvage therapy). [redacted].

Dutt et al. (2021) conducted a retrospective analysis of data from 85 patients with aTTP (including four children) who received caplacizumab in 22 UK hospitals from May 2018 and January 2020. Outcomes for these patients were compared with data from HERCULES and to a group of historical control patients consisting of 39 consecutive cases from the UK TTP registry who received standard treatment (PE plus immunosuppression with corticosteroids and rituximab) from 2014 to 2018.

Efficacy Results

In the RWE cohort of Coppo et al. (2021), the percentage of patients receiving the triplet regimen including caplacizumab with the composite primary outcome including death and refractoriness was 2.2% vs 12.2% in historical controls (HR 6.2, 95% CI 1.4 to 26.3). One patient (1.1%) treated with the triplet regimen died compared with 12 (6.7%) historical controls. One patient (1.1%) treated with the triplet regimen experienced refractory aTTP compared with 16 (18%) historical controls. Compared with historical controls, patients receiving the triplet regimen had numerically fewer PE sessions (median 5 sessions vs 10 sessions), required numerically lower overall PE volume until remission (median 24.2 L vs. 44.2 L), and had numerically shorter duration of hospitalization (median 13 days vs 22 days).

[redacted].

In the RWE cohort of Dutt et al. (2021), five patients (6%) in the caplacizumab cohort died and no deaths were reported among historical control patients. aTTP recurrence and refractoriness were not compared between the two groups. In four of the patients who died, caplacizumab was introduced more than 48 hours after PE initiation (range: 3 to 21 days). Compared with historical controls, patients who received caplacizumab had numerically shorter duration of PE (median 7 days vs. 9 days) and numerically shorter time from PE initiation to platelet count normalization (median 4 days vs 6 days). Duration of hospitalization was similar in the caplacizumab cohort (median 12 days) and the historical control cohort (median 14 days).

Harms Results

The safety data for the RWE cohorts were generally consistent with the clinical trial data from HERCULES. Bleeding events occurred in 12% to 18% of patients. In the RWE cohort of Dutt et al. (2021), five patients (5.9%) experienced venous thromboembolism.

Critical Appraisal

Comparisons between the RWE cohorts and historical controls or the HERCULES trial populations were limited by risk of bias in selection of participants and potential for confounding by measured and unmeasured variables including non-overlapping timeframes and differences in treatment, primarily use of rituximab, which was higher in the RWE cohorts. The impact of bias in selection of patients into RWE cohorts as well as selection of historical control groups could not be evaluated and contributed to a high level of uncertainty. Except for the re-analysis of Sanofi and Cemka (2021), all comparisons were naïve and did not take into account baseline differences between populations, such as cardiac and organ involvement. The rationale for statistical hypothesis testing was not provided and it was unclear whether statistical tests were prespecified or conducted post-hoc for some outcomes. Statistical tests were not adjusted for multiple comparisons and should be interpreted in descriptive and exploratory fashion.

Generalizability of the RWE to Canadian clinical practice was limited by high rates of rituximab use, including as upfront therapy. In addition, in the RWE cohort of Coppo et al. (2021), caplacizumab was administered upfront only, which may not be consistent with the anticipated use of the drug in Canadian clinical practice, according to the clinical experts consulted for this review. In the RWE cohort of Dutt et al. (2021), the baseline characteristics suggested that some had severe disease and/or multiorgan involvement and may have been candidates for upfront therapy with caplacizumab in Canadian practice; however, in approximately half of patients

caplacizumab was started 2 days or longer after PE initiation. In the RWE cohort of Dutt et al. (2021) administration of caplacizumab was not aligned with the HERCULES study or the product monograph due to high rates of discontinuation prior to 30 days post-PE.

Conclusions

Evidence from the HERCULES study suggested that administration of caplacizumab in HERCULES resulted in a statistically significant decrease in the frequency of aTTP recurrence during the HERCULES study period. In the long-term follow-up study of HERCULES (Post-HERCULES), there were no signals that treatment with caplacizumab in HERCULES resulted in increased frequency of aTTP relapse post PE discontinuation beyond the follow-up period of the HERCULES trial. A post-hoc integrated analysis of data from the HERCULES and TITAN trials provided an additional evaluation of survival, healthcare use, organ damage, and refractory aTTP; however, due to naïve pooling of the data and lack of formal statistical testing of prespecified hypothesis including adjustment for multiple comparisons, its results supported but were unable to extend the conclusions regarding these outcomes drawn from the individual trials. Two RWE cohorts from France and the UK provided additional supportive evidence regarding the frequency of aTTP-related events including mortality in patients receiving caplacizumab; however, due to potential for biased patient selection in observational studies, intergroup differences in measured and/or unmeasured confounders including treatments received that could not be accounted for, and absence of formal statistical testing, no conclusions could be drawn that go beyond the HERCULES, Post-HERCULES, and TITAN trial data. The combined data from HERCULES and Post-HERCULES suggested that caplacizumab may decrease overall aTTP recurrence during treatment and immediately following treatment cessation (HERCULES) without producing an increased frequency of long-term aTTP relapse in the subsequent months and years (Post-HERCULES).

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree followed by Markov model
Target population	Adults experiencing an acute aTTP episode
Treatment	Caplacizumab, 11 mg IV injection prior to PEX, followed by 11 mg SC afterwards on Day 1, then 11 mg SC daily following PEX, then 11 mg SC daily for 30 days following the last daily PEX in addition to SoC. If after the initial treatment course, signs of persistent underlying disease such as suppressed ADAMTS13 activity levels remain present, treatment may be extended for a maximum of 28 days.
Dose regimen	Day 1: 11 mg by intravenous (IV) injection at least 15 minutes prior to PEX, followed by 11 mg subcutaneous (SC) injection after completion of PEX Subsequent days: - for duration of PEX: 11 mg daily following PEX administration - post PEX: 11 mg daily for 30 days. Treatment may be extended for a maximum of 28 days if signs of persistent underlying disease remain present.
Submitted price	Caplacizumab, 11 mg, powder for solution: $6,200.0000 per single-use vial
Treatment Costs	$223,200 per single aTTP event (assuming medium duration of therapy as per HERCULES trial)[a]
Comparator	SoC, defined as PEX continuing for at least 2 days after platelet count reaches ≥150 x 10^9/L, corticosteroid treatment of at least 1 mg/kg/day continuing for 1 week after end of PEX, and rituximab as permitted by standard practice at each study centre.
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	Lifetime (53 years)
Key data source	HERCULES trial, post-HERCULES study
Key limitations=	• The long-term probability of relapse is highly uncertain. Evidence from the 3-year post-HERCULES study was used by the sponsor to assume that treatment with caplacizumab for a single aTTP event would convey a life-long benefit in terms of the risk of relapse

Component	Description
	when compared to SoC. However, results from this study were exploratory only and are thus uncertain in the short term, while the lifetime extrapolation of the reduction in relative risk was not considered plausible in CADTH-obtained clinical expert feedback. • The sponsor used as "payoff" approach that was inflexible as it did not allow the recurrence of multiple relapses and oversimplified the modelling of long-term sequelae. Furthermore, the use of prevalence data to estimate long-term sequelae after an individual aTTP event would overestimate the impact of treatment. Together, these increase the uncertainty in the long-term estimates produced by the model. • The assumed duration of neuropsychological impairment is unlikely to be lifelong, as patients would be expected to have improvement or resolution of such symptoms over time. • The relative risk of long-term sequelae for caplacizumab compared with SoC is highly uncertain and modelled results were sensitive to the range of plausible values tested by CADTH. • Poor modelling practices were employed limiting thorough validation of the submitted model. This limits the degree of confidence in the model results.
CADTH reanalysis results	• In CADTH reanalyses, the reduction in the risk of relapse associated with caplacizumab was limited to three years, and the duration of neuropsychological impairment was limited to one year. • CADTH reanalyses resulted in an ICER of $269,158 per QALY (incremental costs: $278,078; incremental QALYs: 1.03). A price reduction of 75% would be required to achieve a $50,000 per QALY threshold. • CADTH was unable to fully address the lack of data regarding the potential reduction in risk of long-term sequelae, and due to inflexibility in the sponsor's submitted model, was unable to explore the impact of treatment on multiple relapses or consider incidence-based rates of long-term sequelae. Together, these issues increase uncertainty in the long-term model extrapolations where the majority of incremental QALYs were gained.

ADAMTS13 = A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aTTP = acquired thrombotic thrombocytopenic purpura; ICER = incremental cost-effectiveness ratio; IV = intravenous; PEX = plasma exchange; QALY= quality-adjusted life-year; SC = subcutaneous; SoC = standard of care.
[a] Based on the median duration of caplacizumab therapy of 35 days in the HERCULES trial (i.e. the median 5 days of PEX therapy plus an additional 30 days).

Budget Impact

CADTH identified the following key limitations with the sponsor's BIA: uncertainties in the annual number of aTTP events, the proportion of caplacizumab use that would be publicly funded and the uptake of caplacizumab. Furthermore, standard of care and downstream cost offsets were not considered for either the drug plan or healthcare system payer perspective. CADTH was unable to address these limitations but made two minor corrections to the sponsor's BIA model on the annual rate of aTTP events as well as updating NIHB population data. In the corrected base-case, the three-year budget impact of reimbursing caplacizumab is $24,925,736. ($6,870,366 in Year 1, $8,294,254 in Year 2, and $9,761,116 in Year 3). Scenario analysis to explore the sensitivity of the budget impact model to the limitations noted above found that the 3-year total budget impact estimates may range from $19,085,852 to $42,008,193.

Canadian Drug Expert Committee (CDEC) Information

Members of the Committee:

CDEC:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Mr. Morris Joseph Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting Date: October 26, 2022

Regrets

None

Conflicts of Interest

None